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FEATURE REVIEW

MR-based *in vivo* hippocampal volumetrics: 2. Findings in neuropsychiatric disorders

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Magnetic resonance imaging (MRI) has opened a new window to the brain. Measuring hippocampal volume with MRI has provided important information about several neuropsychiatric disorders. We reviewed the literature and selected all English-language, human subject, data-driven papers on hippocampal volumetry, yielding a database of 423 records. Smaller hippocampal volumes have been reported in epilepsy, Alzheimer's disease, dementia, mild cognitive impairment, the aged, traumatic brain injury, cardiac arrest, Parkinson's disease, Huntington's disease, Cushing's disease, herpes simplex encephalitis, Turner's syndrome, Down's syndrome, survivors of low birth weight, schizophrenia, major depression, posttraumatic stress disorder, chronic alcoholism, borderline personality disorder, obsessive–compulsive disorder, and antisocial personality disorder. Significantly larger hippocampal volumes have been correlated with autism and children with fragile X syndrome. Preservation of hippocampal volume has been reported in congenital hyperplasia, children with fetal alcohol syndrome, anorexia nervosa, attention-deficit and hyperactivity disorder, bipolar disorder, and panic disorder. Possible mechanisms of hippocampal volume loss in neuropsychiatric disorders are discussed.
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MR-based *in vivo* hippocampal volumetric assessment of the hippocampus has been a widely employed neuroimaging technique in various neuropsychiatric disorders. The hippocampus plays a vital role in processes of memory formation and stress and emotional regulation. Although the functions of the hippocampus are still somewhat elusive, in humans, the hippocampus has been directly implemented in spatial and episodic memory (see Burgess *et al*[1] for a review). Lately, the role of the hippocampus in semantic memory has been elucidated as well.[2,3] In addition, the hippocampus is also involved in novelty processing.[4,5] Within the hippocampus, functional segregation exists, with the left anterior hippocampus processing both behaviourally relevant and behaviourally irrelevant novelty as well as register mismatches between expectation and experience, and the posterior hippocampi processing familiarity.[4,6,7] Regulation of the hypothalamo-pituitary-adrenal (HPA) axis is another important function of the hippocampus.[8]

Glucocorticoid receptors in the hippocampus are activated by rising glucocorticoid levels during stress, in order to mediate fast feedback inhibition of the HPA axis. Stress, hypoxia, and increased glutamate have been associated with damage to the hippocampus, which has increased interest in this area in neuropsychiatric disorders. The hippocampus has been implicated in several neuropsychiatric disorders. Sullivan *et al*[9] examined the extent to which genes and the environment exert differential contributions to hippocampal structural integrity in humans, and showed that the volume of the hippocampus, as measured on MRI, is subject to substantially less genetic control than comparison brain regions. Environmental factors thus play a large role in determining hippocampal morphometry.

The advent of MRI in the last few decades has witnessed an escalation of hippocampal volumetric studies in various neuropsychiatric disorders. The medial temporal limbic area is specifically affected in Alzheimer's disease (AD) and temporal lobe epilepsy (TLE), and hippocampal volumetric assessment has aided in diagnosis and etiology of these disorders.[10,11] Similarly, the psychotic features of schizophrenia have been attributed to

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abnormal hippocampal activity and a disturbance of hippocampal–cortical connections.[12] Work by Sapolsky *et al*[13,14] and others on the effect of glucocorticoids and stress exposure on the hippocampus in rats provided the theoretical framework for hippocampal volumetric studies in stress- and anxiety-related disorders such as depression and posttraumatic stress disorder (PTSD). The noninvasive nature of MR-based volumetric assessment has enabled researchers to assess the nature and longitudinal course of hippocampal volume in numerous other neuropsychiatric disorders as well.

However, studies have used a variety of different research designs and methodologies, and have also come up with (sometimes) inconsistent results. The companion paper (see Geuze *et al*[447]) has focused on the differences in segmentation protocols used. This paper will focus on findings in hippocampal volume in studies across the spectrum of neuropsychiatric disorders, from temporal lobe epilepsy and Huntington's disease, to schizophrenia and PTSD, thus establishing a global overview of hippocampal volumetric findings which may be used to make theoretical assumptions as to what these hippocampal volume reductions actually mean, and how they relate to the etiology and course of these disorders.

Materials and methods

We performed a Medline Indexed search with the keywords 'hippocampus,' 'volume,' and 'MRI.' All the abstracts were carefully scrutinized, and from this database all English-language, human subject, data-driven papers were selected yielding a database of 423 records (only papers published before December 31, 2003 were included). Major advances in MRI hardware and software were implemented from 1988,[15] and thus studies prior to 1988 were not included. In cases, where MRI studies reported data from the same subjects, but used different analyses, both references were included.

Results

The number of MRI hippocampal volumetric studies performed has steadily increased over the last decades, as Figure 1 shows. From 1992 onwards, the number of studies on hippocampal volume increases linearly. This increase stabilizes at approximately 50 studies per year by the year 2000. The increase in studies since 1992 was fuelled by several researchers who have published volumetric protocols and neuroanatomical guidelines which have been adopted by others.[16–21]

Hippocampal volumetric studies have been performed in more than 40 different populations, and are especially popular in disorders such as TLE, schizophrenia, and AD. In our database, these populations have been re-grouped into 34 diagnostic categories (see Table 1). In the majority of these studies a decrease in hippocampal volume was expected, and subsequently found. However, in a large number of neuropsychiatric disorders the data are not always as consistent as in studies with temporal lobe epileptic or AD patients. Although within disorders there is some consistency in the type of protocols that researchers have used, slight variations in each of these protocols may amount to significant differences in their findings (for a review see Geuze *et al*[447]).

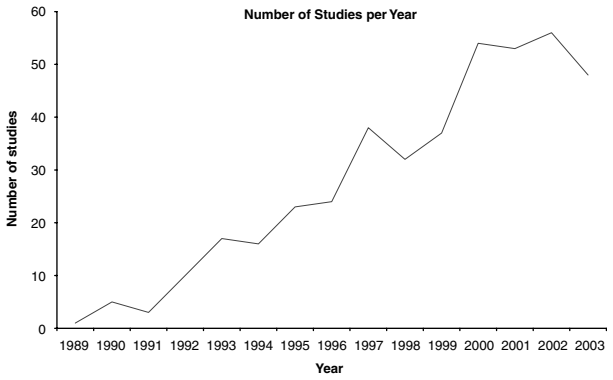

Figure 1 Number of hippocampal volumetric studies with MRI per year from 1989 to 2003.

Temporal lobe epilepsy

In temporal lobe epilepsy hippocampal volumetry has played an important role in the determination of hippocampal sclerosis (HS) or hippocampal atrophy. Significant reduction in hippocampal volumes is used as a specific marker for HS, and right-side minus left-side hippocampal formation volume (DHF) is used to quantify unilateral HF atrophy.[22–31] These methods are superior to visual inspection of MR images.[32] Hippocampal volumetric analysis with MRI is not always able to detect hippocampal sclerosis accurately,[33] however, in those cases the additional analysis of entorhinal cortex volume or volume ratio analysis may be able to provide accurate lateralization of seizure focus (see Bernasconi *et al*[34] and Vossler *et al*,[35] respectively). These methods have demonstrated considerable efficacy, especially with the addition of T2 relaxation time data.[36–41]

Patients with mesial temporal lobe epilepsy exhibit smaller hippocampal volumes.[16,42–47] This hippocampal volume reduction is highly concordant with the side of the epileptogenic focus, and hippocampal deficits are most pronounced ipsilateral to the epileptic focus.[48–52] If amygdala volume reductions are also documented, an additional gain in specificity of seizure lateralization is achieved.[53,54] Quigg *et al*[46] showed that hippocampi contralateral to the epileptic focus are also smaller in TLE than in controls, but larger than hippocampi ipsilateral to the epileptic focus (see also Lambert *et al*[55]). Unilateral hippocampal volume loss and increased T2 value were found in 71% of patients with HS, and bilaterally normal hippocampal volume and T2 value were found in 67% of patients without HS.[36] Within the hippocampus, volume reduction is usually not uniform; the

Table 1 Number of studies in various neuropsychiatric disorders which have examined hippocampal volumes with MRI with some general findings

Disorder	*Number of studies*	*General findings*
Temporal lobe epilepsy	84	↓ Hippocampi, most pronounced ipsilateral to epileptic focus
Schizophrenia	76	↓/↔ Hippocampi bilaterally
Alzheimer's disease	56	↓ Hippocampi bilaterally; marker for temporal lobe degeneration
Normal controls	44	Hippocampal volume is dependent on gender, handedness, and age
Other epilepsy	23	↓ Hippocampi bilaterally
Major depression	20	↔/Recently ↓ hippocampi bilaterally have been demonstrated
Aged	15	Smaller hippocampi are associated with normal aging
PTSD	14	↓/↔ Smaller hippocampi bilaterally
Other dementia	11	↓ Hippocampi
Alcoholism	9	↓/↔ Hippocampi bilaterally
Bipolar disorder	7	↓/↑ Hippocampal volume
Mild cognitive impairment	7	Hippocampal volume loss predictive of conversion to AD
TBI	6	↓ Hippocampi bilaterally
Autism	5	↓/↑ Hippocampal volume
Down's syndrome	5	↓ Hippocampal volume bilaterally
APOE-epsilon 4 allele pos	3	Additionally ↓ hippocampi compared to controls
Borderline personality disorder	3	↓ Hippocampi bilaterally
Febrile seizures	3	↓/↔ Hippocampi
Herpes simplex	3	↓ Hippocampi
Korsakoff's syndrome	3	↓/↔ Hippocampi
OCD	3	↓/↔ Hippocampi bilaterally
Amnesia	2	↓ Hippocampi bilaterally which correlates with impaired memory
Cardiac arrest	2	↓ Hippocampi
Cushing's disease	2	↓ Hippocampi bilaterally; volume increases after treatment
Fragile X syndrome	2	↑ Hippocampi bilaterally
Low birth weight	2	↓ Hippocampi
Panic disorder	2	↔ Hippocampi compared to controls
Parkinson's disease	2	↓ Hippocampi bilaterally
ADHD	1	↔ Hippocampi compared to controls
Anorexia nervosa	1	↔ Hippocampi compared to controls
Antisocial personality disorder	1	Volume of posterior hippocampi negatively correlated to psychopathy
Breast cancer surgery	1	↓ Left hippocampi in women with distressing recollections
Congenital adrenal hyperplasia	1	↔ Hippocampi compared to controls
Fetal alcohol syndrome	1	↔ Hippocampi compared to controls
Huntington	1	↓ Hippocampi bilaterally
Sleep apnea	1	↓ Gray matter concentration in hippocampi
Turner's syndrome	1	↓ Hippocampi bilaterally

↓ = smaller ↑ = larger ↓/↑ = both smaller and larger hippocampal volumes haven been reported ↔ no significant changes ↓/↔ = both smaller and no significant studies have been reported.

hippocampal head is more atrophic than the hippocampal body and hippocampal tail.[56] Lately, several studies have also determined progressive volume loss in mesial TLE.[57,58] Hippocampal volume is correlated with entorhinal cortex volume in TLE,[59] and with flumazenil binding.[60]

A longer epilepsy duration,[61–64] a high number of seizures,[44,65–67] an earlier age of onset,[61,65,66,68] the presence of early aberrant neurological insults such as febrile convulsions,[65,66,68–70] and even gender (men have increased risk of seizure damage),[71] have all been associated with smaller hippocampal volume in TLE. Some discrepancies exist here as well, as some studies have been unable to find a relation between seizure frequency or longer epilepsy duration and hippocampal volume.[72,73] In some studies, satisfactory surgical outcome seems to be related to hippocampal atrophy prior to surgery,[50,74,75] but not in others.[47] Prompt treatment after a status epilepticus may prevent progressive hippocampal volume reduction.[76,77]

The volume reduction witnessed in TLE is the result of neuronal cell death. Lee *et al*[78] compared MRI hippocampal volumes prior to anterior temporal lobectomy with quantitative neuronal density measurements in resected hippocampal specimens and found evidence for a significant correlation of MR-derived hippocampal volume with neuronal density in the CA1, CA2, and CA3 subfields of the hippocampus. This finding has been confirmed by Luby *et al*[75] and Briellmann *et al*[79] who found that the ipsilateral hippocampal volume best predicted the neuronal cell count in the dentate gyrus, whereas the T2 relaxation time, on the other hand, best

predicted the glial cell count in the dentate gyrus (see also Diehl *et al*,[80] Kuzniecky *et al*,[81] and Van Paesschen *et al*[82]). It is not clear whether the neuronal cell death also constitutes functionally relevant tissue, as hippocampal volume loss is not a major determinant of regional hypometabolism in TLE.[83] Although a later study by Theodore *et al*[84] was able to find a significant relation between hippocampal volume and glucose metabolism.

Studies in TLE have also correlated the left hippocampus with verbal memory.[85,86] Trenerry *et al*[87] found that the ratio of the right *vs* left hippocampal volume is significantly correlated with postoperative verbal memory change. Later, they demonstrated that left anterior temporal lobectomy (ATL) patients revealed an expected decrease in verbal memory postoperatively regardless of whether the volumetrically symmetric hippocampi were atrophic.[88] Left temporal lobectomy patients with bilaterally atrophic hippocampi have the poorest verbal memory before and after operation, a finding that has been corroborated by Martin *et al*[89] who showed that patients with left TLE and the presence of bilateral hippocampal atrophy had worse verbal memory before and after ATL compared to patients with unilateral hippocampal atrophy or patients with right TLE and bilateral hippocampal atrophy. Baxendale *et al*[90] demonstrated that patients with smaller remnant hippocampal volumes demonstrated more postoperative memory decline than those with larger remnant hippocampal volume, and that extensive shrinkage of the remnant volume was associated with postoperative memory decline in both right and left ATL patient groups.

Right temporal lobectomy patients tend to have improved verbal memory postoperatively independent of bilateral hippocampal atrophy. Although a relation of hippocampal volume with visual memory has been much harder to find,[85] Baxendale *et al*[91] did show that right hippocampal volume was significantly correlated with delayed recall of a complex figure. Hippocampal asymmetry (right minus left hippocampal volume) is significantly correlated with right minus left intracarotid amobarbital memory scores.[92]

Hippocampal volumetry has also been used to determine region of interest,[93–95] or partial volume correction[96] for PET in temporal lobe epilepsy. A number of studies have also examined methodological issues in hippocampal volumetry in epilepsy such as, optimizing hippocampal volume determination,[17,97] the necessity of hippocampal volume normalization,[98–100] the comparability and reliability of manual and digitizer measurements,[49] the correlation of hippocampal body with total hippocampal volume,[101] the intra- and interobserver variability,[102] and the utility of automated methods.[31,103]

In summary, hippocampal volumetry with MRI is primarily utilized in the determination of hippocampal atrophy and hippocampal sclerosis. Pre- and postoperative hippocampal volumes are correlated with neurophysiological, neuropathological, neuropsychological, and clinical findings, as well as surgical outcome.[30] The presence of decreased hippocampal volume in TLE has been correlated with decreased verbal memory pre- and postoperatively. Several studies have also evaluated the link between hippocampal volume and other predictors with outcome measures of ATL.

Other epilepsy

In patients with porencephaly-related seizures, bilateral amygdala–hippocampal atrophy exists in the presence of unilateral cysts.[104] Reduced hippocampal volume, or loss of volume asymmetry has also been found in partial epilepsy,[105,106] and childhood epilepsy.[107,108] Voxel-by-voxel comparison of brain regions in juvenile myoclonic epilepsy and TLE failed to show hippocampal atrophy in either disorder.[109] Hippocampal volumetry data in temporal lobe epilepsy should be corrected for total brain volume, as this is the largest predictor of hippocampal volume.[110]

Traumatic brain injury

Arciniegas *et al*[111] reported significantly smaller hippocampal volume bilaterally in traumatic brain injury (TBI) patients compared to matched normal control subjects. In two large samples of 94 and 118 patients with TBI, Bigler *et al*[112,113] showed that TBI patients had bilaterally smaller hippocampi compared to normal controls. In three cases of TBI acquired at birth, at age 4, and at age 9, 3D volumetric MRI revealed bilateral hippocampal volume reduction 13-15 years after the occurrence of TBI.[114] This volume reduction is not always related to the severity of the injury. No significant volume differences were found in mild *vs* severe TBI.[115] In a morphometric study before and after anterior cingulotomy significantly smaller bilateral hippocampi were not found.[116]

Alzheimer's disease

In Alzheimer's disease (AD) hippocampal volume loss is a hallmark of the disorder.[117,118–130] Smaller hippocampal volume is also present in mild AD,[131,132] in African Americans with AD,[133] and is more pronounced in those AD patients who carry the epsilon 4 allele[134–136] (for an exception see Bigler *et al*[137]). A study comparing mild AD patients with nondemented controls using large-deformation high-dimensional brain mapping found significant volume loss over time and different patterns of hippocampal shape change over time, that distinguished mild AD from healthy aging.[138] Although hippocampal volume loss is not specific to AD, volume loss is more severely manifested in AD than in other dementias.[139–141] There is one study, however, where hippocampal volume loss present in demented Parkinson's disease (PD) patients, was significantly worse than the volume loss exhibited in AD patients.[142] The hippocampal volume loss in AD has been shown to be related to the degree of

neurophysiological activity as measured by magnetoencephalography.[143]

Researchers have found that hippocampal volume loss is able to discriminate patients and controls accurately, and that age- and gender-adjusted, normalized MRI-based hippocampal volumetric measurements provide a sensitive marker of the mesial temporal lobe neuroanatomic degeneration in AD.[121,144–146] However, use of hippocampal volume exclusively is not advocated by all authors,[147–149] and other structures such as the amygdala and the entorhinal cortex may also need to be measured,[150–153] or hippocampal *N*-acetyl aspartate measurements may need to be performed to improve diagnosis.[154] Karas *et al*[155] performed voxel-based morphometric analysis in AD and found volume loss of other structures to be equally predictive of AD. Others have provided evidence that assessment of delayed recall with the Visual Reproduction Test is of high diagnostic accuracy, even surpassing hippocampal volumetry.[156] Despite the theoretical rationale for the superiority of entorhinal measurements in early AD, Xu *et al*,[157] present evidence that measurements of the hippocampus and entorhinal cortex were approximately equivalent at intergroup discrimination. Because of the ambiguity surrounding entorhinal cortex measurement, measurements of the hippocampus may actually be preferable due to superior reproducibility of the measurements. Age transformation may provide an easily applicable method to increase the clinical diagnostic accuracy of hippocampal measurements by considering the effect of aging on hippocampus volume.[158] Progressive measurements of hippocampal volume loss provide some additional information, but do not increase the discriminating power significantly.[159] Very accurate volumetric measurements of the whole hippocampal formation can be obtained by MRI, which strongly correlates with neuronal numbers, and suggest a high anatomical validity of magnetic resonance imaging volume measurements.[160]

In AD patients, the volumes of the left hippocampus correlated significantly with the Mini Mental State Examination score and with immediate and delayed verbal memory; the smaller the volume the more impaired the memory performance.[124] Other researchers have found a similar correlation between memory performance and hippocampal volume decline.[161–164] Kohler *et al*[165] also examined this relation and found that hippocampal volume correlated positively with delayed, but not immediate recall of a verbal auditory list learning task. In normal controls there was a trend towards a negative association between hippocampal volumes and delayed verbal recall. De Toledo-Morrell *et al*[166] showed that left hippocampal volume was the best predictor of free recall and delayed free recall of verbal information, and that recall and delayed recall of the spatial location of verbal items were best predicted by right hippocampal volume. They also showed a differential effect, as this relation between hippocampal volume and memory function observed in cases with AD did not hold for healthy aged control subjects. Some research groups have not been able to link hippocampal volume loss with either severity of memory impairment,[167] or general or emotional memory performance.[168]

In several studies, decreased hippocampal volume has been shown to be a risk factor for AD.[169–173] Individuals carrying the apolipoprotein E epsilon 4 allele (APOE-epsilon 4 allele) are at high risk for developing AD. The presence of a single APOE-epsilon 4 allele is associated with an increased rate of hippocampal volume loss in healthy women in their sixth decade of life that is not related to any detectable memory changes.[174] Similarly, nondemented elderly subjects carrying the APOE-epsilon 4 allele display decreased hippocampal volume symmetry on MRIs.[175] MRI measurements of hippocampal volume begin to decrease in conjunction with memory decline in cognitively normal persons at risk for Alzheimer's disease,[176] and the rate of hippocampal volume loss correlates with change in clinical status.[177]

The determination of hippocampal volume in AD may be reliably and consistently assessed across different research centers.[178] Crum *et al*[179] and Gosche *et al*[180] have examined automated methods of deriving hippocampal volumetry and found them to be equally reliable to manual segmentation methods in AD. The finding of a strong relationship between left hippocampal volume and performance on odor identification tasks is compatible with left-hemisphere superiority for verbally mediated olfactory tasks, suggesting a neural substrate for the breakdown in functional performance on verbally mediated odor identification tasks in AD.[181]

Dementia

Studies of hippocampal volume have also been performed in dementias other than AD. In a study comparing demented patients with cognitive impairment subjects and elderly controls, demented patients showed the greatest annual rates of volume loss in the hippocampus and cortex.[182] This volume loss was also significantly greater in demented patients compared with both cognitive impaired and elderly control subjects. Similarly, Grunwald *et al*[183] found hippocampal volume loss in dementia, and Barber *et al*[184] found a loss of hippocampal asymmetry in patients with dementia with Lewy bodies (DLB) (as well as AD patients) compared to normal controls. Volumetric MRI of the brain in elderly subjects with lacunes, mild cognitive impairment, a group of patients with dementia, and a group with probable AD revealed hippocampal volume loss in all three patient groups.[185] Du *et al*[186] assessed hippocampal volume loss in cognitively normal subjects, patients with subcortical ischemic vascular dementia, and patients with AD. Patients with subcortical ischemic vascular dementia had smaller hippocampi than cognitively normal subjects, but larger hippocampi than patients with AD. Voxel-based morphometric

analysis of patients with semantic dementia and a group of age-matched normal controls did not find evidence of significantly smaller hippocampi.[187] In a study comparing global and regional atrophy on MRI in subjects with DLB, AD, vascular dementia, and normal aging, subjects with DLB had significantly larger temporal lobe, hippocampal, and amygdala volumes than those with AD.[188] No significant volumetric difference between subjects with DLB and vascular dementia was observed. The first study to use voxel-based morphometry to assess hippocampal volume in DLB showed preservation of hippocampal volume relative to AD.[189] Bigler *et al*[190] found a significant relationship between hippocampal volume loss and performance on the Mini-Mental-State-Examination Questionnaire. In patients with semantic dementia (the temporal variant of frontotemporal dementia), there was no significant positive correlation between recollection and volume of the hippocampus.[191] For temporal horn and hippocampal volume determination, corrections with total brain volume rather than total intracranial volume may provide more clinically meaningful corrections.[192]

Mild cognitive impairment

In line with investigations in AD, our database also includes studies which have specifically examined hippocampal volume in mild cognitive impairment (MCI). MCI is a transitional state between the cognitive changes of normal aging and AD, in which persons experience unacceptable memory loss, without meeting criteria for AD.[193] Heterogeneity in the use of the term MCI is significant, so it is important to recognize diagnostic criteria that studies use. One of the first studies measured volumes of the hippocampus in age-associated cognitive impairment subjects (as defined by criteria from Crook *et al*[194])and age- and sex-matched controls, and did not find evidence of smaller hippocampal volume,[20] although the volumetric asymmetry between the right and left hippocampi was reduced in age-associated cognitive impairment subjects. Another earlier study investigated hippocampal atrophy in normals, patients with AD, and minimally impaired individuals (with a MMSE $>$ 23, Global Deterioration Scale (GDS) of 3), Clinical Dementia Rating (CDR) of 0.5).[195] Significantly smaller hippocampi differentiated the minimally impaired individuals from the control group. People with mild cognitive impairment are at a higher risk for developing AD. An investigation by Jack *et al*[196] revealed that hippocampal volume loss determined by premorbid MRI volumetric analysis is predictive of subsequent conversion to AD, a finding that was corroborated by others.[130,197,198] Convit *et al*[199] also assessed the ability of medial temporal lobe volume loss to predict decline of MCI to AD and found that addition of baseline medial occipitotemporal, and the combined middle and inferior temporal gyri as predictors increased overall classification accuracy and sensitivity. Encoding en retrieval memory deficits in patients with amnestic MCI, as defined by criteria from Petersen *et al*,[193] are correlated with declines in hippocampal grey matter density.[200]

Aged

Smaller hippocampi have been associated with normal aging[201–209] (in contrast to Sullivan *et al*[210]), and may even constitute a risk factor for the development of dementia.[211,212] In a sample of elderly persons, MR derived hippocampal volume was correlated with delayed memory performance.[213] In another sample of elderly people with suspected normal pressure hydrocephalus, the volume of the hippocampus was correlated with MMSE scores.[214] Elderly women experience greater hippocampal volume loss than aged men.[215] In a large sample study, den Heijer *et al*[216] found that higher plasma homocysteine levels, which are associated with AD, are correlated with smaller hippocampi in the elderly. Sullivan *et al*[9] examined the balance of environmental and genetic effects on hippocampal size in a large sample of elderly twin men and provide evidence that only 40% of the hippocampal volume variance was attributable to genetic influences. In nondemented elderly subjects, hippocampal head size has been related to verbal memory performance.[217]

Estrogen seems to have a neuroprotective effect.[218,219] A recent study by Eberling *et al*[220] compared hippocampal volume in women taking estrogen replacement therapy (ERT) with matched controls. Women taking ERT had larger right hippocampal volumes and bilateral anterior hippocampal volumes than women not taking ERT. However, another recent study investigating the relation between endogenous estradiol levels found that aged women with higher total estradiol levels had smaller hippocampal volumes and poorer memory performance.[221]

Autism

The first volumetric MRI studies in autism did not reveal a significant hippocampal volume reduction in autistic individuals when compared to normal control subjects.[222,223] However, when corrected for whole brain volume, Aylward *et al*[224] were able to find evidence of significant hippocampal volume loss. Similarly, a study comparing high-functioning autistic and normal school-age boys, all with normal intelligence, found that the hippocampus–amygdala complex appeared to be relatively smaller in the autistic than in the typically developing brain.[225] In contrast to all these reports, Sparks *et al*[226] reported significantly increased hippocampal volumes in young children with autism spectrum disorder bilaterally when compared to age-matched control groups of typically developing and developmentally delayed children.

Down's syndrome

Raz *et al*[227] examined neuroanatomic abnormalities in adults with Down's syndrome (DS) and revealed

that DS subjects had substantially smaller hippocampal formations compared to sex-matched healthy control subjects, a finding that was corroborated by others.[228–230] A similar study with a larger number of subjects revealed decreased left hippocampal volume in adults with DS compared to healthy controls.[231] In a study examining both demented and nondemented DS subjects, all DS subjects revealed significantly smaller hippocampi than controls.[232] Non-demented Down's syndrome adults have an age-related decrease of hippocampus volume, which is not found in age-matched healthy comparison subjects.[230] Children with Down's syndrome also display smaller hippocampi bilaterally.[229]

Schizophrenia

Volumetric studies of the hippocampus constitute the second largest diagnostic category in the database with a total of 76 hippocampal volumetric MRI studies in patients with schizophrenia, patients with first-episode schizophrenia, and in relatives of patients with schizophrenia. Smaller bilateral hippocampi in schizophrenia have been found by a large number of research groups.[233–247] This reduction in volume is related to symptom severity.[248] Luchins *et al*[249] was only able to provide evidence of smaller bilateral hippocampi in patients with schizophrenia *and* hypo-osmolemia. A twin study by Baare *et al*[250] revealed that twins discordant for schizophrenia had smaller hippocampal volumes compared to healthy twin pairs, irrespective of zygosity. Becker *et al*[251] and Narr *et al*[252] reported smaller bilateral posterior hippocampi in patients with schizophrenia. Others found evidence for a smaller anterior amygdala-hippocampal complex and anterior hippocampus bilaterally in schizophrenia, respectively.[253,254]

Some studies were only able to find evidence for significantly smaller left hippocampal volume.[255–257] Stefanis *et al*[258] found evidence for smaller left hippocampi only in patients with schizophrenia and birth complications. Others have failed to find any evidence of smaller hippocampi in patients with schizophrenia, compared to controls.[52,259–270] Meta analysis of hippocampal volumetric studies in schizophrenia concluded that schizophrenia was associated with bilateral hippocampal volume loss.[271]

Lately new techniques, such as hippocampal shape analysis in schizophrenia patients are providing some interesting results.[252] Csernansky *et al*[272] shows that shape analysis reveal differences between patients with schizophrenia and controls in the absence of volumetric changes. Similarly, in another study they were not able to find significant hippocampal volume changes in patients with schizophrenia and comparison subjects, but did provide evidence for abnormal hippocampal shape and asymmetry in schizophrenia.[261] Shenton *et al*[273] also showed that shape analysis may provide group discrimination in schizophrenia. Velakoulis *et al*[246] provided evidence that the volume loss behind the head of the hippocampus is discriminating for schizophrenia. Wang *et al*[274] also found that the hippocampal asymmetry was different in schizophrenia.

Other hippocampal volumetric studies in schizophrenia have also been performed. De Lisi *et al*[275] performed a longitudinal study in chronic schizophrenia and found a progressive decrease in size of the amygdala-hippocampal complex over time. In a treatment study, Arango *et al*[276] found that there was no significant difference in hippocampal volume between schizophrenia patients treated with haloperidol *vs* patients treated with clozapine.

There are now several studies investigating hippocampal volumetry in first-episode (FE) schizophrenia. Studying FE schizophrenia is important because confounds such as chronic illness and chronic medication are absent. Bogerts *et al*[277] and Kubicki *et al*[278] found evidence of a smaller left hippocampus in FE patients compared to controls. Hirayasu *et al*[279] found smaller left posterior amygdala hippocampal complex volumes, and Velakoulis *et al*[247] found an additional left hippocampal volume reduction in FE-schizophrenia compared to chronic schizophrenia. Others found smaller hippocampal volume bilaterally,[280,281] or smaller bilateral anterior hippocampi.[282–284] However, other studies did not find any significant hippocampal volume reduction in FE schizophrenia.[264,285–289] Both Wood *et al*[290] and Lieberman *et al*[283] performed longitudinal studies in FE schizophrenia. They did not find progressive hippocampal volume loss over time. Szeszko *et al*[291] investigated neuropsychological correlates of smaller hippocampi in FE schizophrenia. Among men, worse executive and motor functioning correlated significantly with smaller anterior hippocampal volume. Among women, no relationship between neuropsychological variables and either posterior or anterior hippocampal volumes was found.

Several studies have also assessed hippocampal volumes in childhood-onset schizophrenia. However, whereas some studies have shown reduction of the left hippocampus after a 2-year follow-up in comparison to controls,[292] or bilateral hippocampal volume loss over time,[293] others did not find smaller hippocampi in early-onset schizophrenia,[294,295] although it seems that normal hippocampal asymmetry (right greater than left) is lacking in childhood-onset schizophrenia.[294,296] Barta *et al*[297] examined hippocampal volumes in patients with late-onset schizophrenia, AD, and normal elderly controls. They found that patients with late-onset schizophrenia had significantly smaller left hippocampi in comparison to the healthy controls.

In individuals at high risk for developing schizophrenia, researchers have found smaller bilateral hippocampi,[298,299] as well as no significant hippocampal volumetric changes.[300] A study comparing schizophrenia patients with subjects at high risk for developing schizophrenia and controls, found that the left amygdala–hippocampal complex was smaller in FE schizophrenia than in the high-risk

group, which had smaller left amygdala–hippocampal complexes than controls.[301] Hippocampal volume and shape analysis showed that the hippocampi of unaffected siblings of schizophrenia subjects are smaller and that the head of the hippocampi are deformed compared to controls.[302] The unaffected siblings' hippocampi were indistinguishable from schizophrenic subjects.

Major depression

Several studies have examined hippocampal volumetry with MRI in MD. An early MRI volumetric study was unable to find evidence of a significantly smaller amygdala–hippocampal complex in depressed patients.[303] Comorbid hypercortisolemia does not significantly influence hippocampal volume either.[304] Lately, studies have found smaller bilateral hippocampal volume in patients with a first episode of depression, and a past history (multiple episodes) of depression, respectively, compared to controls.[305–307] These last findings have been corroborated by MacQueen *et al*,[308] who compared hippocampal volumes in depressed subjects experiencing a post pubertal onset of depression with matched healthy control subjects, and found that only depressed subjects with multiple depressive episodes had hippocampal volume reductions.

Statistically significant smaller left hippocampal volumes were found in patients with multiple episodes of depression currently treated with antidepressant medication,[309] and in patients with treatment-resistant depression.[310] Voxel-based morphometry in chronic depressed patients revealed reduced grey matter density in the left hippocampus, which was correlated with measures of verbal memory.[311] Others did not observe any significant differences in hippocampal volumes of patients with major depression and control subjects.[312,313] In an effort to explain the inconsistencies in hippocampal volume findings in prior morphometric studies of MD, Vythilingam *et al*[314] assessed hippocampal volume in depressed subjects with and without childhood abuse, as well as in control subjects. Depressed subjects with childhood abuse had an 18% smaller mean left hippocampal volume than the nonabused depressed subjects and a 15% smaller mean left hippocampal volume than the healthy subjects.

Posener *et al*[315] used high-dimensional mapping of the hippocampus to quantitatively characterize size and shape of the hippocampus in patients with MD and controls. While the depressed patients and comparison subjects did not differ in hippocampal volume, there were highly significant group differences in hippocampal shape. In a treatment study, Sheline *et al*[316] investigated the effect of antidepressant treatment on hippocampal volume in MD, and found that longer durations during which depressive episodes went untreated with antidepressant medication were associated with reductions in hippocampal volume, suggesting that antidepressants may have a neuroprotective effect in MD.

Kim *et al*[317] found no amygdala–hippocampal complex volumetric differences in deluded depressed geriatric patients *vs* nondeluded depressed geriatric patients. In other studies on geriatric depression, Steffens *et al*[318] found that patients tended to have smaller bilateral hippocampal volumes compared to controls, whereas Bell-McGinty *et al*[319] demonstrated smaller right hippocampal volumes in geriatric depression. Hsieh *et al*[320] expanded this finding and showed that subjects with small right hippocampal volumes were less likely to achieve remission. Smaller left hippocampal volumes in geriatric depression seem to be a risk factor for developing dementia.[321] Although significantly smaller hippocampi were not found in one study of pediatric patients with MD, volumetric MRI has revealed significantly increased amygdala-hippocampal volume ratios in pediatric MD.[322] A very recent study in a small sample of pediatric patients with MD did reveal decreased hippocampal volumes bilaterally.[323] However, in this study a slightly older population of patients was used.

Bipolar disorder

Swayze *et al*[267] compared bipolar patients with controls and found a significantly smaller right hippocampus in bipolar patients. Later hippocampal volumetric studies conducted in bipolar patients did not find significantly smaller hippocampal volumes in bipolar patients *vs* controls.[324–326] Later studies were also unable to find significant hippocampal volume reductions between bipolar patients and normal controls regardless of the number of episodes.[327,328] Increased right hippocampal volumes associated with poorer neuropsychological functioning in bipolar patients have been reported in two studies which did not include a control group.[329,330]

Posttraumatic stress disorder

The first study of hippocampal volume in PTSD by Bremner *et al*[331] provided evidence that combat-related PTSD patients had statistically significantly smaller right hippocampal volumes relative to that of comparison subjects. Other studies found evidence of significant bilateral hippocampal volume loss in combat-related PTSD,[332] or in PTSD patients with various traumas.[333] In childhood physical and sexual abuse related PTSD, Bremner *et al*[334] reported a decrease in left hippocampal volume in comparison with matched controls. Stein *et al*,[335] who examined hippocampal volume in women with sexual abuse, and matched controls without abuse, also found significantly smaller left hippocampi. Bilateral hippocampal volume was significantly smaller in a small sample study of substance and alcohol naïve subjects with combat-related PTSD compared to controls.[336] In monozygotic twins discordant for trauma exposure, Gilbertson *et al*[337] revealed that the identical nonexposed twins of PTSD combat veterans had comparable hippocampi to their PTSD twin, but significantly smaller hippocampi than combat veterans without PTSD and their noncombat exposed twins, showing

that smaller hippocampi may constitute a risk factor for the development of stress-related psychopathology.

Contrary to all these positive findings of hippocampal volume loss in PTSD, a study assessing hippocampal volume in recent trauma victims did not find evidence of hippocampal volume loss in recent survivors of trauma who later developed PTSD, both within 2 weeks of the trauma, and 6 months after the event compared to other trauma survivors.[338] Although 6 months might be too short a time in which to see hippocampal volumetric changes. Another small sample study examining female victims of intimate partner violence with and without posttraumatic stress disorder was unable to find evidence of smaller hippocampal volume.[339] Schuff *et al*[340] and Neylan *et al*[341] were also unable to find significantly smaller hippocampal volume in patients with PTSD compared to controls, although patients with PTSD did display a significant reduction in *N*-acetylaspartate in the hippocampus bilaterally. In chronic alcoholics with PTSD hippocampal volume was not additionally reduced.[342]

Recently, it has also been shown that women with childhood sexual abuse and PTSD have smaller hippocampi than women with PTSD but without childhood sexual abuse, or than women without PTSD but with childhood sexual abuse.[343] Long-term treatment with paroxetine is associated with increased hippocampal volumes and improvement of verbal declarative memory in PTSD.[344] In a recent study with voxel-based morphometry, Yamasue *et al*[345] did not find evidence of hippocampal volume loss in PTSD. In contrast to the findings in adult PTSD, children with PTSD do not exhibit smaller hippocampi in comparison with matched controls[346–349] (see Table 2).

Chronic alcoholism

A study by Sullivan *et al*[350] revealed bilateral anterior hippocampal volume loss in men with chronic alcoholism compared to healthy male control subjects. Agartz *et al*[342] examined hippocampal volume in chronic alcoholics and compared this to overall brain volume. They found that in chronic alcoholism, the reduction of hippocampal volume is proportional to the reduction of whole brain volume. Another study also provided evidence of significantly reduced hippocampal volumes in chronic alcoholics compared to controls.[351] Laakso *et al*[352] compared hippocampal volume in late- onset type 1 alcoholics to early-onset type 2 alcoholics, as well as in normal volunteers. Compared to the controls, the right, but not left, hippocampi were significantly smaller in both alcoholic groups, even after controlling for intracranial volume. De Bellis *et al*[353] found significantly smaller bilateral hippocampi in subjects with alcohol abuse disorders compared to comparison subjects.

Recently, pathologically raised levels of plasma homocysteine have been shown to be significantly correlated to smaller hippocampi.[354] In addition, the presence of an association between hippocampal volume reduction and first-onset alcohol withdrawal seizure was examined. They found the average hippocampal volumes measured by high-resolution MRI to be significantly reduced in alcoholics compared with healthy controls, but found no correlation with seizures[355] confirming results of an earlier study by Sullivan *et al*[356] A study by Di Sclafani *et al*[357] investigated hippocampal volumes in crack-cocaine, crack-cocaine/alcohol-dependent subjects, and age-matched controls, but did not find any hippocampal differences between the three groups.

Other disorders

There are a number of studies which have investigated hippocampal volumes in other neuropsychiatric disorders. The results of these studies are summarized in Table 3. Decreased hippocampal volumes have been reported in borderline personality disorder, in obsessive-compulsive disorder, in cardiac arrest, in Cushing's disease, in herpes simplex encephalitis, in Parkinson's disease, in Huntington's disease, in Turner's syndrome, and in survivors of low birth weight. Children with fragile X syndrome display significantly increased hippocampal volumes. In panic disorder, in anorexia nervosa, in congenital hyperplasia, in children with fetal alcohol

Table 2 Hippocampal volumetric findings in pediatric and adult manifestations of various neuropsychiatric disorders

Population	*Pediatric*	*Adult*
Epilepsy	↓ Hippocampi bilaterally	↓ Hippocampi bilaterally
Schizophrenia	↔ In hippocampal volume	↓ Hippocampi bilaterally
Depression	↔ In hippocampal volume; larger amydala: hippocampus ratios in depressed subjects	↓ Hippocampi bilaterally
PTSD	↔ In hippocampal volume	↓ Hippocampi bilaterally
TBI	↓ Hippocampi bilaterally	↓ Hippocampi bilaterally
Autism	↓/↑ Hippocampi bilaterally	↓ Hippocampi bilaterally
Down's syndrome	↓ Hippocampi bilaterally	↓ Hippocampi bilaterally

↓ = smaller ↑ = larger ↓/↑ = both smaller and larger hippocampal volumes haven been reported ↔ no significant changes ↓/↔ = both smaller and no significant studies have been reported.

syndrome, and in attention-deficit and hyperactivity disorder hippocampal volume is preserved.

Normal controls

In several studies with normal control subjects, the right hippocampus has been found to be larger than the left hippocampus,[19,358,359] although this difference may not always reach significance.[360] This asymmetry is also present in children.[361] Szabo *et al*[362] compared amygdala and hippocampal volume measurements bilaterally between right- and left-handed participants. Right-to-left volume ratios differed significantly between right- and left-handed participants for both amygdala and hippocampus.

In children, hippocampi may also be measured reliably (see Obenaus *et al*[363] for a detailed protocol). Developmental aspects of the hippocampus in children have been examined.[364,365] In developing children aged 4–18, the hippocampus increases with age.[364] Pfluger *et al*[366] developed normative volumetric data of the developing hippocampus in children.

Hippocampal volumes are also subject to gender differences. Bhatia *et al*[201] found evidence for smaller left hippocampi in women. Others also reported that the volume of the hippocampal formation was larger in men than in women.[99,367] Contrary to this, a study by Filipek *et al*[368] reported that women have larger hippocampi than men. Two other studies were not able to find gender differences in hippocampal volume.[369,370] Similarly, gender did not affect right-to-left amygdala and hippocampal volume ratios in right- or left-handed participants.[362] In men, the hippocampus declines with age, starting in the third life decade.[371] From the age of 54, hippocampal volume starts to decline at an increased rate (compared to total brain atrophy) in both men and women.[372]

Several studies performed in healthy subjects have examined the relation of hippocampal volume to IQ and memory. Full-scale IQ is significantly related to hippocampal volume,[373] and left hippocampal volume is negatively associated with the level of delayed verbal recall performance.[374] Bilateral hippocampal volume corrected for whole brain volume is negatively correlated with explicit memory,[375] but not with motor performance.[376] In related work, Maguire *et al*[377] showed that the posterior hippocampi of London taxi drivers were significantly larger relative to those of control subjects, and that this volume correlated with the amount of time spent as a taxi driver, but was not related with innate navigational expertise.[378] These data provided evidence for the theory that the posterior hippocampus stores a spatial representation of the environment and has the ability to expand regionally in order to accommodate elaboration of this representation in people with a high dependence on navigational skills.

Methodological issues related to hippocampal volumetry have been ironed out with healthy controls. Several studies have used healthy controls to assess the reliability of new manual tracing protocols,[18,21,363,379–383] point-counting methods,[384] or automated segmentation techniques.[385–387] Other studies have looked at specific methodological issues, such as magnetic field strength,[379,388,389] hippocampal orientation,[390] the use of reformatted 3D images,[391] the effect of slice thickness,[392] handedness,[362] and economical means of acquiring hippocampal volumes.[393]

Discussion

In epilepsy research and in temporal lobe epilepsy in particular, hippocampal volumetry with MRI is primarily utilized in the determination of hippocampal atrophy and hippocampal sclerosis. In addition, researchers have correlated pre- and postoperative hippocampal volumes with neurophysiological, neuropathological, neuropsychological, and clinical findings, as well as surgical outcome.[30] The hippocampal sclerosis and hippocampal atrophy present in mesial TLE is indicative of the epileptogenic focus and is related to neuronal cell death. A large number of predisposing, maintaining, and exacerbating factors of hippocampal atrophy in TLE have also been established. The presence of decreased hippocampal volume in TLE has been correlated with decreased verbal memory pre- and postoperatively. In addition, the ratio between right and left hippocampal volume, as well as gender, is correlated with postoperative verbal memory.[394] Several studies have also evaluated the link between hippocampal volume and other predictors with outcome measures of ATL.

An important issue in TLE is whether seizures are the cause or the result of hippocampal sclerosis. Kalviainen and Salmenpera,[65] who sought to answer this question by using MRI to investigate the appearance of medial temporal lobe damage during the course of partial epilepsy, and, particularly, to determine whether recurrent or prolonged seizures contribute to the atrophy, provided evidence that hippocampal damage may indeed be both cause *and* consequence of TLE. This debate is by no means resolved, although longitudinal studies which allow determination of cerebral damage *when* it occurs, as well as new MRI techniques such as diffusion tensor imaging may provide answers.[395] Longitudinal studies are ongoing in patients with newly diagnosed and chronic epilepsy, with an interscan interval of 3.5 years, using complementary voxel- and region-based methods that can detect changes in hippocampal and cerebellar volumes of 3%.

In AD, hippocampal volume loss is a manifested morphological abnormality of the disease. Some studies have also shown that decreased hippocampal volume may also be a risk factor for developing AD. Generally it is assumed that hippocampal volume loss is able to discriminate patients and controls, especially when combined with entorhinal cortex and temporal neocortical volume.[10] The reduced hippocampal volume present in these patients is related to MMSE scores and memory performance.

Table 3 Hippocampal volumetric findings in various neuropsychiatric disorders

Population	*Study*	*Subjects*	*Finding*
Borderline personality disorder	Driessen *et al*[418]	21 female patients with BPD, and 21 healthy controls	Bilateral hippocampal volume reduction
	Schmahl *et al*[412]	10 patients with BPD, and 23 control subjects	Bilateral hippocampal volume reduction
	Tebartz van Elst *et al*[419]	8 unmedicated female patients with BPD, and 8 matched healthy controls	Bilateral hippocampal volume reduction
Febrile seizures	Szabo *et al*[420]	5 children 22–68 months old, and 11 controls, 15–83 months old	Reduced hippocampal volume in children with CFS, and right to left ratios greater than 1 in all 5 children with CFS compared to controls
	Tarkka *et al*[421]	24 patients with a prolonged first febrile seizure, 8 with an unprovoked seizure after the first febrile seizure, and 32 age-, sex-, and handedness-matched control subjects	Mean total volumes of the right and left hippocampal formations did not differ significantly between any of the three groups
	Scott *et al*[325]	14 patient with prolonged febrile seizures	Hippocampal volume reduction, and significant increase in hippocampal volume asymmetry
Herpes simplex	Yoneda *et al*[422]	5 post- herpes simplex encephalitic (post-HSE) patients with temporal lobe damage and memory impairment, and 10 age-matched control subjects	Two patients had a marked atrophy of the hippocampal formation, 3 patients had larger hippocampi
	Caparros-Lefebvre *et al*[423]	11 patients with clinically presumed HSVE, and 5 matched controls	Hippocampal volume reduction
	Colchester *et al*[424]	11 Korsakoff's syndrome, 9 herpes encephalitis, 6 focal frontal lesion patients, and 10 healthy controls	Hippocampal volume reduction present in herpes encephalitis
Korsakoff's syndrome	Visser *et al*[425]	13 subjects with Korsakoff's syndrome, 13 subjects with chronic alcoholism without Korsakoff's syndrome, and 13 control subjects	Reduced hippocampal volume in Korsakoff's syndrome compared to subjects with chronic alcoholism and healthy controls
	Colchester *et al*[424]	11 Korsakoff's syndrome, 9 herpes encephalitis, 6 focal frontal lesion patients, and 10 healthy controls	No reduction in hippocampal volume in Korsakoff's syndrome.
	Sullivan *et al*[426]	5 Korsakoff's syndrome, 20 AD, 36 healthy controls	Bilateral hippocampal volume deficits in Korsakoff's syndrome and AD compared to controls
OCD	Jenike *et al*[427]	10 female patients with OCD, and 10 matched female control subjects	No significant differences
	Szeszko *et al*[428]	26 patients with OCD, and 26 healthy comparison subjects	OCD patients lacked the normal hemispheric asymmetry of the hippocampus–amygdala complex.
	Kwon *et al*[242]	22 patients with OCD, 22 patients with schizophrenia, and 22 normal subjects	Hippocampal volume was bilaterally reduced in both OCD and schizophrenic patients *vs* the normal controls
Amnesia	Kopelman *et al*[429]	40 patients with organic amnesia, and 10 healthy controls	Loss of hippocampal volume correlates significantly with impaired memory performance
	Isaacs *et al*[430]	10 adolescents with a diagnosis of developmental amnesia (DA), 11 adolescents born preterm (PT), and 8 age-matched normal controls	Bilateral reduction in hippocampal volume in the two patient groups with DA significantly < PT significantly < controls
Cardiac arrest	Fujioka *et al*[416]	11 vegetative patients after cardiac arrest, and 22 healthy matched controls	Bilateral hippocampal volume reduction

	Grubb *et al*[431]	17 out-of-hospital cardiac arrest survivors, and 12 patients with uncomplicated myocardial infarction	Left amygdala–hippocampal volume was reduced in memory-impaired OHCA victims compared with control subjects
Cushing's disease	Starkman *et al*[432]	12 patients with Cushing's disease	Reduced hippocampal formation volume
	Starkman *et al*[433]	22 patients with Cushing's disease	Increased hippocampal formation volume after treatment
Fragile X syndrome	Reiss *et al*[415]	15 fragile X subjects and 26 age- and IQ-matched control subjects.	Hippocampal volumes in children with fragile X were significantly increased bilaterally
	Kates *et al*[434]	6 fragile X subjects and 7 normal controls	Hippocampal volumes in children with fragile X were significantly increased
Low birth weight	Peterson *et al*[435]	25 eight-year-old preterm children, and 39 matched term control children	Bilateral hippocampal volume reduction in preterm children compared to controls
	Abernethy *et al*[413]	87 children (aged 15–16 years) with a history of very low birth weight (<1500 g), and 8 age-matched full-term controls	Children with a low IQ had smaller left hippocampi, and a smaller hippocampal ratio (left volume:right volume) than those with normal IQ
Panic disorder	Vythilingam *et al*[436]	13 patients with panic disorder, and 14 healthy subjects	No hippocampal volume reduction
	Uchida *et al*[437]	11 patients with panic disorder, and 11 matched controls	No significant hippocampal volume reduction
Parkinson's disease	Camicioli *et al*[438]	10 patients with PD, 10 with PD and dementia or mild cognitive impairment, 11 with Alzheimer's disease, 12 control subjects	Bilateral hippocampal volume reduction in all patient groups compared to controls
	Laakso *et al*[142]	50 patients with AD, 9 patients with vascular dementia, 12 patients with PD without dementia, 8 patients with PD and dementia, and 34 elderly control subjects.	Significant reduction of hippocampal volume in all patient groups compared to controls
ADHD	Castellanos *et al*[439]	57 boys with ADHD, and 55 healthy matched controls	No hippocampal volume reduction
Antisocial personality disorder	Laakso *et al*[440]	18 male violent offenders with antisocial personality disorder	Volume of the bilateral posterior hippocampus was negatively correlated with scores on the Psychopathy Checklist-Revised (which measures the degree of psychopathy).
Anorexia nervosa	Giordano *et al*[441]	20 AN females, and age-matched healthy female controls	No significant difference was found between right and left HAF in both patients and CG
Breast cancer surgery	Nakano *et al*[442]	67 women who had had breast cancer surgery 3 or more years earlier and had no history of PTSD or major depression before the cancer	The volume of the left hippocampus was significantly smaller in the subjects with a history of distressing cancer-related recollections ($N=28$) than in those without any such history ($N=39$). There was no significant difference in right hippocampal volume or whole brain volume measured as a control
Congenital adrenal hyperplasia	Merke *et al*[443]	27 children with CAH, and 47 sex- and age-matched controls	No hippocampal volume reduction
Fetal alcohol syndrome	Archibald *et al*[444]	14 FAS, 12 patients with prenatal exposure to alcohol, and 41 healthy controls	No hippocampal volume reduction
Huntington's disease	Rosas *et al*[445]	18 patients with HD, and 18 age-matched healthy controls	Bilateral hippocampal volume reduction in HD compared to controls
Sleep apnea	Morrell *et al*[446]	7 male patients with obstructive sleep apnea, 7 age- and handedness-matched male controls	Significantly lower grey matter concentration within the left hippocampus
Turner's syndrome	Murphy *et al*[414]	18 women with TS, and 19 healthy age-matched women	Bilateral hippocampal volume reduction in TS compared to controls

Hippocampal volume declines with age, and hippocampal volume loss is generally present in demented patients, and in mild cognitive impairment. Traumatic brain injury is also associated with bilateral hippocampal volume loss. In mild cognitive impairment, the hippocampal volume loss has been shown to be an early marker for developing AD later.[196,197]

In schizophrenia, abundant evidence exists which points to smaller bilateral hippocampal volume that is associated with both chronic and first-episode schizophrenia,[12,271] although the exact nature of the smaller hippocampi is still a contested issue. Whether these hippocampal volume losses are progressive or developmental are issues which longitudinal MRI studies will address.[275,396] Some recent studies have emphasized the need for future research to pay more attention to the issue of shape analysis, as this has provided more consistent results and may provide group discrimination in schizophrenia.[246,272,273] In individuals at high risk for developing schizophrenia and first-degree relatives of patients with schizophrenia, smaller hippocampi are also present.

Proton magnetic resonance spectroscopy studies in schizophrenia have reported low *N*-acetyl-aspartate levels of the hippocampus,[262,397,398] which is also present in the unaffected relatives of patients with schizophrenia.[399] The subtle volume reductions found in schizophrenia and the presence of smaller hippocampi early in the course of the disease seems to argue against a neurodegenerative mechanism in schizophrenia. The presence of hippocampal pathology in relatives of schizophrenic probands may point to a genetic risk factor instead.[12,299] Research with both monozygotic and dizygotic twins has shown that smaller hippocampal volumes are present in both the healthy twin and the twin with schizophrenia providing additional evidence that smaller hippocampal volumes are a genetic risk factor for schizophrenia,[250,302] although additional decreases in hippocampal volume following onset of psychosis may augment the developmental impairment.[400,401] In a review article of studies which have assessed hippocampal pathology with different modalities, Weinberger[402] postulates that genes involved in the formation and maintenance of hippocampal circuitry play a role in susceptibility. In rats, it has been shown that not only neonatal excitotoxic lesions disrupt development of the prefrontal cortex, but that transient inactivation of the ventral hippocampus during a critical period of development may also produce subtle anatomical changes in the hippocampus, sufficient to disrupt normal maturation of the prefrontal cortex (and perhaps, other interconnected late maturing regions).[403] Recently, it was demonstrated that schizophrenia (as well as bipolar disorder) was associated with a reduction of key oligodendrocyte-related and myelin-related genes, showing that connectivity issues will play an important role in unravelling the mystery of schizophrenia and other psychosis-related disorders.[404]

In animal research, an extensive literature abounds, which has shown that prolonged exposure to stress or glucocorticoids, has adverse effects on the rodent hippocampus.[405] Hippocampal volume loss in Cushing's disease, which is characterized by a pathologic oversecretion of glucocorticoids; major depression, often associated with hypersecretion of glucocorticoids; and PTSD have been theorized to be the result of glucocorticoid excess.[405,406] Although stress is not always associated with elevated cortisol levels,[407] this does not preclude the possibility that elevated levels of cortisol at the time of trauma (which we are unable to measure) are associated with hippocampal damage.[408] PTSD patients exhibit significantly higher cortisol levels during and shortly after traumatic script exposure compared to controls, which is consistent with elevated cortisol levels at time of initial trauma exposure.[409] Heightened sensitivity of the glucocorticoid receptor, associated with PTSD, has also been shown to lead to hippocampal volume loss, and this may also explain the volume loss present in PTSD.[8,407] Another possible explanation is that smaller hippocampi may constitute a risk factor for the development of stress-related psychopathology.[337] However, long-term treatment with paroxetine is associated with increased hippocampal volumes and improvement of verbal declarative memory in PTSD, and this makes it unlikely that genetic factors are exclusively responsible for smaller hippocampal volume in PTSD.[344]

Failure of adult neurogenesis in patients with MD has been proposed to constitute the biological and cellular basis of this disorder.[410,411] In patients with depression and childhood abuse, smaller hippocampi could also be explained by elevated cortisol levels at time of trauma. Patients with Cushing's disease exhibit reduced hippocampal volumes which are associated with the pathological oversecretion of cortisol. In patients with borderline personality disorder and childhood abuse, the reduction in hippocampal volume has been theorized to be the result of increased glucocorticoid levels, reduced levels of brain-derived neurotrophic factors, and inhibition of neurogenesis, due to early life stress exposure.[412] Increased levels of glucocorticoids have also been thought to be accountable for smaller hippocampal volume in individuals who survived very low birth weight without major disability.[413] Cardiac arrest and herpes simplex encephalitis have also been associated with smaller hippocampi. In a study with patients who had undergone breast cancer surgery, the volume of the left hippocampus was significantly smaller in the subjects with a history of distressing cancer-related recollections than in those without such a history.

In alcoholism hippocampal volume loss may reflect general brain atrophy present in chronic alcoholism as the hippocampal volume loss is proportional to general reduction of brain volume.[342] Increased packing density of small immature neurons with truncated dendritic development indicative of curtailment in

the development of the neurons and neuropil are proposed to be responsible for the hippocampal volume decrease in autism.[224] In Down and Turner's syndrome, hippocampal volume loss has been related to developmental abnormalities, but the exact mechanisms are still unclear.[229,414] Increased hippocampal volume in individuals with fragile X syndrome, may result from neurotoxins, subclinical seizures or kindling, denervation of afferent pathways, abnormalities of the cellular–neurochemical–receptor interaction, or a combination of these factors.[415]

Brief cardiac arrest is typically followed by transient global ischemia, which leads to delayed neuronal cell death and has been suggested to underlie the hippocampal volume loss witnessed in humans with cardiac arrest.[416] In Parkinson's disease it has been proposed that demise of the entorhinal cortex in PD (through the presence of neurofibrillary tangles) isolates the hippocampus from its isocortical inputs and thus causes volume loss.[142] In Huntington's disease, a similar explanation may hold, as the entorhinal region is atrophied in HD as well.[417]

In studies specifically performed in healthy controls, it has been shown that the right hippocampus is larger than the left. Hippocampal volumes are also subject to right- and left-handedness, to gender, and to age. The hippocampus has been directly implemented in spatial,[1] episodic,[1] and even semantic memory in humans.[2,3] In addition, the hippocampus is also involved in novelty processing,[4,5] and stress regulation.[8] A lot of the methodological ground work for reliably measuring hippocampal volumes has been performed in healthy subjects, and has helped straighten out several methodological issues.

Future directions

Although there are still obvious discrepancies in the research findings in a large number of these disorders, conflicting results and methodological issues are being resolved. Greater consistency may be achieved in the future with the introduction of reliable automated methods of hippocampal volume determination. The use of MRI-derived hippocampal volume is a proven method with diagnostic value, which is also used in the determination of etiology and course of neuropsychiatric diseases. As such it is an indispensable technique and further studies are needed to focus research on unraveling the mechanisms of hippocampal volume loss in these disorders. Additional neuroimaging techniques such as diffusion tensor imaging, magnetization transfer imaging, magnetic resonance spectroscopy, shape analysis, functional magnetic resonance imaging, receptor imaging with PET, and functional connectivity analysis are vital instruments in achieving these goals.

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References

1 Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. *Neuron* 2002; **35**: 625–641.
2 Bayley PJ, Hopkins RO, Squire LR. Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. *Neuron* 2003; **38**: 135–144.
3 Manns JR, Hopkins RO, Squire LR. Semantic memory and the human hippocampus. *Neuron* 2003; **38**: 127–133.
4 Strange B, Dolan R. Functional segregation within the human hippocampus. *Mol Psychiatry* 1999; **4**: 508–511.
5 Vinogradova OS. Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. *Hippocampus* 2001; **11**: 578–598.
6 Strange BA, Fletcher PC, Henson RN, Friston KJ, Dolan RJ. Segregating the functions of human hippocampus. *Proc Natl Acad Sci USA* 1999; **96**: 4034–4039.
7 Strange BA, Dolan RJ. Adaptive anterior hippocampal responses to oddball stimuli. *Hippocampus* 2001; **11**: 690–698.
8 Hoschl C, Hajek T. Hippocampal damage mediated by corticosteroids–a neuropsychiatric research challenge. *Eur Arch Psychiatry Clin Neurosci* 2001; **251**(Suppl 2): II81–II88.
9 Sullivan EV, Pfefferbaum A, Swan GE, Carmelli D. Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. *Hippocampus* 2001; **11**: 754–762.
10 Chetelat G, Baron JC. Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. *Neuroimage* 2003; **18**: 525–541.
11 Jack Jr CR. Medial temporal lobe volumetrics in traumatic brain injury. *AJNR Am J Neuroradiol* 1997; **18**: 25–28.
12 Heckers S. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus* 2001; **11**: 520–528.
13 Sapolsky RM. A mechanism for glucocorticoid toxicity in the hippocampus: increased neuronal vulnerability to metabolic insults. *J Neurosci* 1985; **5**: 1228–1232.
14 Sapolsky RM, Krey LC, McEwen BS. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. *J Neurosci* 1985; **5**: 1222–1227.
15 Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res* 2001; **49**: 1–52.
16 Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. *Brain* 1992; **115**(Part 4): 1001–1015.
17 Jack Jr CR. MRI-based hippocampal volume measurements in epilepsy. *Epilepsia* 1994; **35**(Suppl 6): S21–S29.
18 Jack Jr CR, Bentley MD, Twomey CK, Zinsmeister AR. MR imaging-based volume measurements of the hippocampal formation and anterior temporal lobe: validation studies. *Radiology* 1990; **176**: 205–209.
19 Jack Jr CR, Twomey CK, Zinsmeister AR, Sharbrough FW, Petersen RC, Cascino GD. Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. *Radiology* 1989; **172**: 549–554.
20 Soininen HS, Partanen K, Pitkanen A, Vainio P, Hanninen T, Hallikainen M *et al.* Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. *Neurology* 1994; **44**: 1660–1668.
21 Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A *et al.* Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology* 1992; **42**: 1743–1750.
22 Adam C, Baulac M, Saint-Hilaire JM, Landau J, Granat O, Laplane D. Value of magnetic resonance imaging-based measurements of hippocampal formations in patients with partial epilepsy. *Arch Neurol* 1994; **51**: 130–138.
23 Ashtari M, Barr WB, Schaul N, Bogerts B. Three-dimensional fast low-angle shot imaging and computerized volume measurement of the hippocampus in patients with chronic epilepsy of the temporal lobe. *AJNR Am J Neuroradiol* 1991; **12**: 941–947.

24 Bernasconi N, Bernasconi A, Caramanos Z, Andermann F, Dubeau F, Arnold DL. Morphometric MRI analysis of the parahippocampal region in temporal lobe epilepsy. *Ann N Y Acad Sci* 2000; **911**: 495–500.
25 Bernasconi A, Cendes F, Lee J, Reutens DC, Gotman J. EEG background delta activity in temporal lobe epilepsy: correlation with volumetric and spectroscopic imaging. *Epilepsia* 1999; **40**: 1580–1586.
26 Cascino GD, Jack CRJr Parisi JE, Marsh WR, Kelly PJ, Sharbrough FW *et al.* MRI in the presurgical evaluation of patients with frontal lobe epilepsy and children with temporal lobe epilepsy: pathologic correlation and prognostic importance. *Epilepsy Res* 1992; **11**: 51–59.
27 Jack Jr CR, Sharbrough FW, Twomey CK, Cascino GD, Hirschorn KA, Marsh WR *et al.* Temporal lobe seizures: lateralization with MR volume measurements of the hippocampal formation. *Radiology* 1990; **175**: 423–429.
28 Paterson A, Winder J, Bell KE, McKinstry CS. An evaluation of how MRI is used as a pre-operative screening investigation in patients with temporal lobe epilepsy. *Clin Radiol* 1998; **53**: 353–356.
29 Tien RD, Felsberg GJ, Campi de Castro C, Osumi AK, Lewis DV, Friedman AH *et al.* Complex partial seizures and mesial temporal sclerosis: evaluation with fast spin-echo MR imaging. *Radiology* 1993; **189**: 835–842.
30 Watson C, Jack Jr CR, Cendes F. Volumetric magnetic resonance imaging. Clinical applications and contributions to the understanding of temporal lobe epilepsy. *Arch Neurol* 1997; **54**: 1521–1531.
31 Webb J, Guimond A, Eldridge P, Chadwick D, Meunier J, Thirion JP *et al.* Automatic detection of hippocampal atrophy on magnetic resonance images. *Magn Reson Imaging* 1999; **17**: 1149–1161.
32 Reutens DC, Stevens JM, Kingsley D, Kendall B, Moseley I, Cook MJ *et al.* Reliability of visual inspection for detection of volumetric hippocampal asymmetry. *Neuroradiology* 1996; **38**: 221–225.
33 Jackson GD, Kuzniecky RI, Cascino GD. Hippocampal sclerosis without detectable hippocampal atrophy. *Neurology* 1994; **44**: 42–46.
34 Bernasconi N, Bernasconi A, Caramanos Z, Dubeau F, Richardson J, Andermann F *et al.* Entorhinal cortex atrophy in epilepsy patients exhibiting normal hippocampal volumes. *Neurology* 2001; **56**: 1335–1339.
35 Vossler DG, Kraemer DL, Knowlton RC, Kjos BO, Rostad SW, Wyler AR *et al.* Temporal ictal electroencephalographic frequency correlates with hippocampal atrophy and sclerosis. *Ann Neurol* 1998; **43**: 756–762.
36 Briellmann RS, Jackson GD, Kalnins R, Berkovic SF. Hemicranial volume deficits in patients with temporal lobe epilepsy with and without hippocampal sclerosis. *Epilepsia* 1998; **39**: 1174–1181.
37 Mackay CE, Webb JA, Eldridge PR, Chadwick DW, Whitehouse GH, Roberts N. Quantitative magnetic resonance imaging in consecutive patients evaluated for surgical treatment of temporal lobe epilepsy. *Magn Reson Imaging* 2000; **18**: 1187–1199.
38 Van Paesschen W, Connelly A, King MD, Jackson GD, Duncan JS. The spectrum of hippocampal sclerosis: a quantitative magnetic resonance imaging study. *Ann Neurol* 1997; **41**: 41–51.
39 Van Paesschen W, Duncan JS, Stevens JM, Connelly A. Longitudinal quantitative hippocampal magnetic resonance imaging study of adults with newly diagnosed partial seizures: one-year follow-up results. *Epilepsia* 1998; **39**: 633–639.
40 Van Paesschen W, Sisodiya S, Connelly A, Duncan JS, Free SL, Raymond AA *et al.* Quantitative hippocampal MRI and intractable temporal lobe epilepsy. *Neurology* 1995; **45**: 2233–2240.
41 Woermann FG, Barker GJ, Birnie KD, Meencke HJ, Duncan JS. Regional changes in hippocampal T2 relaxation and volume: a quantitative magnetic resonance imaging study of hippocampal sclerosis. *J Neurol Neurosurg Psychiatry* 1998; **65**: 656–664.
42 DeCarli C, Hatta J, Fazilat S, Fazilat S, Gaillard WD, Theodore WH. Extratemporal atrophy in patients with complex partial seizures of left temporal origin. *Ann Neurol* 1998; **43**: 41–45.
43 Jutila L, Ylinen A, Partanen K, Alafuzoff I, Mervaala E, Partanen J *et al.* MR volumetry of the entorhinal, perirhinal, and temporopolar cortices in drug-refractory temporal lobe epilepsy. *AJNR Am J Neuroradiol* 2001; **22**: 1490–1501.
44 Kalviainen R, Salmenpera T, Partanen K, Vainio P, Riekkinen P, Pitkanen A. Recurrent seizures may cause hippocampal damage in temporal lobe epilepsy. *Neurology* 1998; **50**: 1377–1382.
45 Lawson JA, Vogrin S, Bleasel AF, Cook MJ, Bye AM. Cerebral and cerebellar volume reduction in children with intractable epilepsy. *Epilepsia* 2000; **41**: 1456–1462.
46 Quigg M, Bertram EH, Jackson T. Longitudinal distribution of hippocampal atrophy in mesial temporal lobe epilepsy. *Epilepsy Res* 1997; **27**: 101–110.
47 Quigg M, Bertram EH, Jackson T, Laws E. Volumetric magnetic resonance imaging evidence of bilateral hippocampal atrophy in mesial temporal lobe epilepsy. *Epilepsia* 1997; **38**: 588–594.
48 Bernasconi N, Bernasconi A, Andermann F, Dubeau F, Feindel W, Reutens DC. Entorhinal cortex in temporal lobe epilepsy: a quantitative MRI study. *Neurology* 1999; **52**: 1870–1876.
49 Hoshida T, Sakaki T, Morimoto T, Hashimoto H, Kurokawa S, Nakase H *et al.* Manual and digitizer measurements of amygdalohippocampal volume: reliability in comparison to computer-based measurement. *Psychiatry Clin Neurosci* 1995; **49**: S223–S225.
50 Jack Jr CR, Sharbrough FW, Cascino GD, Hirschorn KA, O'Brien PC, Marsh WR. Magnetic resonance image-based hippocampal volumetry: correlation with outcome after temporal lobectomy. *Ann Neurol* 1992; **31**: 138–146.
51 Marsh L, Morrell MJ, Shear PK, Sullivan EV, Freeman H, Marie A *et al.* Cortical and hippocampal volume deficits in temporal lobe epilepsy. *Epilepsia* 1997; **38**: 576–587.
52 Marsh L, Sullivan EV, Morrell M, Lim KO, Pfefferbaum A. Structural brain abnormalities in patients with schizophrenia, epilepsy, and epilepsy with chronic interictal psychosis. *Psychiatry Res* 2001; **108**: 1–15.
53 Cendes F, Andermann F, Gloor P, Evans A, Jones-Gotman M, Watson C *et al.* MRI volumetric measurement of amygdala and hippocampus in temporal lobe epilepsy. *Neurology* 1993; **43**: 719–725.
54 Cendes F, Leproux F, Melanson D, Ethier R, Evans A, Peters T *et al.* MRI of amygdala and hippocampus in temporal lobe epilepsy. *J Comput Assist Tomogr* 1993; **17**: 206–210.
55 Lambert MV, Brierley B, Al-Sarraj S, Shaw P, Polkey CE, Chandler C *et al.* Quantitative magnetic resonance imaging of the amygdala in temporal lobe epilepsy-clinico-pathological correlations (a pilot study). *Epilepsy Res* 2003; **53**: 39–46.
56 Bernasconi N, Bernasconi A, Caramanos Z, Antel SB, Andermann F, Arnold DL. Mesial temporal damage in temporal lobe epilepsy: a volumetric MRI study of the hippocampus, amygdala and parahippocampal region. *Brain* 2003; **126**: 462–469.
57 Briellmann RS, Berkovic SF, Syngeniotis A, King MA, Jackson GD. Seizure-associated hippocampal volume loss: a longitudinal magnetic resonance study of temporal lobe epilepsy. *Ann Neurol* 2002; **51**: 641–644.
58 Fuerst D, Shah J, Shah A, Watson C. Hippocampal sclerosis is a progressive disorder: a longitudinal volumetric MRI study. *Ann Neurol* 2003; **53**: 413–416.
59 Salmenpera T, Kalviainen R, Partanen K, Pitkanen A. Quantitative MRI volumetry of the entorhinal cortex in temporal lobe epilepsy. *Seizure* 2000; **9**: 208–215.
60 Lamusuo S, Pitkanen A, Jutila L, Ylinen A, Partanen K, Kalviainen R *et al.* Flumazenil binding in the medial temporal lobe in patients with temporal lobe epilepsy: correlation with hippocampal MR volumetry, T2 relaxometry, and neuropathology. *Neurology* 2000; **54**: 2252–2260.
61 Fuerst D, Shah J, Kupsky WJ, Johnson R, Shah A, Hayman-Abello B *et al.* Volumetric MRI, pathological, and neuropsychological progression in hippocampal sclerosis. *Neurology* 2001; **57**: 184–188.
62 Jokeit H, Ebner A, Arnold S, Schuller M, Antke C, Huang Y *et al.* Bilateral reductions of hippocampal volume, glucose metabolism, and wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy. *J Neurol* 1999; **246**: 926–933.
63 Seeck M, Lazeyras F, Murphy K, Naimi A, Pizzolatto GP, de Tribolet N *et al.* Psychosocial functioning in chronic epilepsy:

relation to hippocampal volume and histopathological findings. *Epileptic Disord* 1999; **1**: 179–185.
64 Spencer SS, McCarthy G, Spencer DD. Diagnosis of medial temporal lobe seizure onset: (relative specificity and sensitivity of quantitative MRI. *Neurology* 1993; **43**: 2117–2124.
65 Kalviainen R, Salmenpera T. Do recurrent seizures cause neuronal damage? A series of studies with MRI volumetry in adults with partial epilepsy. *Prog Brain Res* 2002; **135**: 279–295.
66 Salmenpera T, Kalviainen R, Partanen K, Pitkanen A. Hippocampal and amygdaloid damage in partial epilepsy: a cross-sectional MRI study of 241 patients. *Epilepsy Res* 2001; **46**: 69–82.
67 Saukkonen A, Kalviainen R, Partanen K, Vainio P, Riekkinen P, Pitkanen A. Do seizures cause neuronal damage? A MRI study in newly diagnosed and chronic epilepsy. *Neuroreport* 1994; **6**: 219–223.
68 Trenerry MR, Jack Jr CR, Sharbrough FW, Cascino GD, Hirschorn KA, Marsh WR *et al.* Quantitative MRI hippocampal volumes: association with onset and duration of epilepsy, and febrile convulsions in temporal lobectomy patients. *Epilepsy Res* 1993; **15**: 247–252.
69 Barr WB, Ashtari M, Schaul N. Bilateral reductions in hippocampal volume in adults with epilepsy and a history of febrile seizures. *J Neurol Neurosurg Psychiatry* 1997; **63**: 461–467.
70 Keller SS, Wieshmann UC, Mackay CE, Denby CE, Webb J, Roberts N. Voxel based morphometry of grey matter abnormalities in patients with medically intractable temporal lobe epilepsy: effects of side of seizure onset and epilepsy duration. *J Neurol Neurosurg Psychiatry* 2002; **73**: 648–655.
71 Briellmann RS, Berkovic SF, Jackson GD. Men may be more vulnerable to seizure-associated brain damage. *Neurology* 2000; **55**: 1479–1485.
72 Cendes F, Andermann F, Gloor P, Lopes-Cendes I, Andermann E, Melanson D *et al.* Atrophy of mesial structures in patients with temporal lobe epilepsy: cause or consequence of repeated seizures? *Ann Neurol* 1993; **34**: 795–801.
73 Spanaki MV, Kopylev L, Liow K, DeCarli C, Fazilat S, Gaillard WD *et al.* Relationship of seizure frequency to hippocampus volume and metabolism in temporal lobe epilepsy. *Epilepsia* 2000; **41**: 1227–1229.
74 Jack Jr CR, Trenerry MR, Cascino GD, Sharbrough FW, So EL, O'Brien PC. Bilaterally symmetric hippocampi and surgical outcome. *Neurology* 1995; **45**: 1353–1358.
75 Luby M, Spencer DD, Kim JH, deLanerolle N, McCarthy G. Hippocampal MRI volumetrics and temporal lobe substrates in medial temporal lobe epilepsy. *Magn Reson Imaging* 1995; **13**: 1065–1071.
76 Liu RS, Lemieux L, Bell GS, Sisodiya SM, Bartlett PA, Shorvon SD *et al.* The structural consequences of newly diagnosed seizures. *Ann Neurol* 2002; **52**: 573–580.
77 Salmenpera T, Kalviainen R, Partanen K, Mervaala E, Pitkanen A. MRI volumetry of the hippocampus, amygdala, entorhinal cortex, and perirhinal cortex after status epilepticus. *Epilepsy Res* 2000; **40**: 155–170.
78 Lee N, Tien RD, Lewis DV, Friedman AH, Felsberg GJ, Crain B *et al.* Fast spin-echo, magnetic resonance imaging-measured hippocampal volume: correlation with neuronal density in anterior temporal lobectomy patients. *Epilepsia* 1995; **36**: 899–904.
79 Briellmann RS, Kalnins RM, Berkovic SF, Jackson GD. Hippocampal pathology in refractory temporal lobe epilepsy: T2-weighted signal change reflects dentate gliosis. *Neurology* 2002; **58**: 265–271.
80 Diehl B, Najm I, Mohamed A, Babb T, Ying Z, Bingaman W. Interictal EEG hippocampal atrophy, and cell densities in hippocampal sclerosis and hippocampal sclerosis associated with microscopic cortical dysplasia. *J Clin Neurophysiol* 2002; **19**: 157–162.
81 Kuzniecky R, Palmer C, Hugg J, Martin R, Sawrie S, Morawetz R *et al.* Magnetic resonance spectroscopic imaging in temporal lobe epilepsy: neuronal dysfunction or cell loss? *Arch Neurol* 2001; **58**: 2048–2053.
82 Van Paesschen W, Revesz T, Duncan JS, King MD, Connelly A. Quantitative neuropathology and quantitative magnetic resonance imaging of the hippocampus in temporal lobe epilepsy. *Ann Neurol* 1997; **42**: 756–766.
83 O'Brien TJ, Newton MR, Cook MJ, Berlangieri SU, Kilpatrick C, Morris K *et al.* Hippocampal atrophy is not a major determinant of regional hypometabolism in temporal lobe epilepsy. *Epilepsia* 1997; **38**: 74–80.
84 Theodore WH, Gaillard WD, De Carli C, Bhatia S, Hatta J. Hippocampal volume and glucose metabolism in temporal lobe epileptic foci. *Epilepsia* 2001; **42**: 130–132.
85 Martin RC, Hugg JW, Roth DL, Bilir E, Gilliam FG, Faught E *et al.* MRI extrahippocampal volumes and visual memory: correlations independent of MRI hippocampal volumes in temporal lobe epilepsy patients. *J Int Neuropsychol Soc* 1999; **5**: 540–548.
86 Pegna AJ, Caldara-Schnetzer AS, Perrig SH, Lazeyras F, Khateb A, Mayer E *et al.* Is the right amygdala involved in visuospatial memory? Evidence from MRI volumetric measures. *Eur Neurol* 2002; **47**: 148–155.
87 Trenerry MR, Jack Jr CR, Ivnik RJ, Sharbrough FW, Cascino GD, Hirschorn KA *et al.* MRI hippocampal volumes and memory function before and after temporal lobectomy. *Neurology* 1993; **43**: 1800–1805.
88 Trenerry MR, Jack Jr CR, Cascino GD, Sharbrough FW, So EL. Bilateral magnetic resonance imaging-determined hippocampal atrophy and verbal memory before and after temporal lobectomy. *Epilepsia* 1996; **37**: 526–533.
89 Martin RC, Sawrie SM, Knowlton RC, Bilir E, Gilliam FG, Faught E *et al.* Bilateral hippocampal atrophy: consequences to verbal memory following temporal lobectomy. *Neurology* 2001; **57**: 597–604.
90 Baxendale SA, Thompson PJ, Kitchen ND. Postoperative hippocampal remnant shrinkage and memory decline: a dynamic process. *Neurology* 2000; **55**: 243–249.
91 Baxendale SA, van Paesschen W, Thompson PJ, Connelly A, Duncan JS, Harkness WF *et al.* The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia* 1998; **39**: 158–166.
92 Baxendale SA, Van Paesschen W, Thompson PJ, Duncan JS, Shorvon SD, Connelly A. The relation between quantitative MRI measures of hippocampal structure and the intracarotid amobarbital test. *Epilepsia* 1997; **38**: 998–1007.
93 Koepp MJ, Hammers A, Labbe C, Woermann FG, Brooks DJ, Duncan JS. 11C-flumazenil PET in patients with refractory temporal lobe epilepsy and normal MRI. *Neurology* 2000; **54**: 332–339.
94 Koepp MJ, Richardson MP, Brooks DJ, Poline JB, Van Paesschen W, Friston KJ *et al.* Cerebral benzodiazepine receptors in hippocampal sclerosis. *An objective in vivo analysis. Brain* 1996; **119**(Part 5): 1677–1687.
95 Szelies B, Weber-Luxenburger G, Mielke R, Pawlik G, Kessler J, Pietrzyk U *et al.* Interictal hippocampal benzodiazepine receptors in temporal lobe epilepsy: comparison with coregistered hippocampal metabolism and volumetry. *Eur J Neurol* 2000; **7**: 393–400.
96 Koepp MJ, Richardson MP, Labbe C, Brooks DJ, Cunningham VJ, Ashburner J *et al.* 11C-flumazenil PET, volumetric MRI, and quantitative pathology in mesial temporal lobe epilepsy. *Neurology* 1997; **49**: 764–773.
97 Liu RS, Lemieux L, Bell GS, Bartlett PA, Sander JW, Sisodiya SM *et al.* A longitudinal quantitative MRI study of community-based patients with chronic epilepsy and newly diagnosed seizures: methodology and preliminary findings. *Neuroimage* 2001; **14**: 231–243.
98 Free SL, Li LM, Fish DR, Shorvon SD, Stevens JM. Bilateral hippocampal volume loss in patients with a history of encephalitis or meningitis. *Epilepsia* 1996; **37**: 400–405.
99 Free SL, Bergin PS, Fish DR, Cook MJ, Shorvon SD, Stevens JM. Methods for normalization of hippocampal volumes measured with MR. *AJNR Am J Neuroradiol* 1995; **16**: 637–643.
100 King D, Spencer SS, McCarthy G, Luby M, Spencer DD. Bilateral hippocampal atrophy in medial temporal lobe epilepsy. *Epilepsia* 1995; **36**: 905–910.
101 Kim JH, Tien RD, Felsberg GJ, Osumi AK, Lee N. MR measurements of the hippocampus for lateralization of temporal lobe

epilepsy: value of measurements of the body *vs* the whole structure. *AJR Am J Roentgenol* 1994; **163**: 1453–1457.
102 Achten E, Deblaere K, De Wagter C, Van Damme F, Boon P, De Reuck J *et al.* Intra- and interobserver variability of MRI-based volume measurements of the hippocampus and amygdala using the manual ray-tracing method. *Neuroradiology* 1998; **40**: 558–566.
103 Hogan RE, Mark KE, Wang L, Joshi S, Miller MI, Bucholz RD. Mesial temporal sclerosis and temporal lobe epilepsy: MR imaging deformation-based segmentation of the hippocampus in five patients. *Radiology* 2000; **216**: 291–297.
104 Ho SS, Kuzniecky RI, Gilliam F, Faught E, Bebin M, Morawetz R. Congenital porencephaly: MR features and relationship to hippocampal sclerosis. *AJNR Am J Neuroradiol* 1998; **19**: 135–141.
105 Baulac M, De Grissac N, Hasboun D, Oppenheim C, Adam C, Arzimanoglou A *et al.* Hippocampal developmental changes in patients with partial epilepsy: magnetic resonance imaging and clinical aspects. *Ann Neurol* 1998; **44**: 223–233.
106 Martinez M, Santamaria J, Mercader JM, Catafau A, Cardenal C, Lomena F. Correlation of MRI hippocampal volume analysis, video/EEG monitoring and inter- and postictal single photon emission tomography in refractory focal epilepsy. *Neuroradiology* 1994; **36**: 11–16.
107 Grunewald RA, Farrow T, Vaughan P, Rittey CD, Mundy J. A magnetic resonance study of complicated early childhood convulsion. *J Neurol Neurosurg Psychiatry* 2001; **71**: 638–642.
108 Lawson JA, Cook MJ, Bleasel AF, Nayanar V, Morris KF, Bye AM. Quantitative MRI in outpatient childhood epilepsy. *Epilepsia* 1997; **38**: 1289–1293.
109 Woermann FG, Free SL, Koepp MJ, Ashburner J, Duncan JS. Voxel-by-voxel comparison of automatically segmented cerebral gray matter—A rater-independent comparison of structural MRI in patients with epilepsy. *Neuroimage* 1999; **10**: 373–384.
110 Lawson JA, Vogrin S, Bleasel AF, Cook MJ, Burns L, McAnally L *et al.* Predictors of hippocampal, cerebral, and cerebellar volume reduction in childhood epilepsy. *Epilepsia* 2000; **41**: 1540–1545.
111 Arciniegas DB, Topkoff JL, Rojas DC, Sheeder J, Teale P, Young DA *et al.* Reduced hippocampal volume in association with p50 nonsuppression following traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 2001; **13**: 213–221.
112 Bigler ED, Anderson CV, Blatter DD, Andersob CV. Temporal lobe morphology in normal aging and traumatic brain injury. *AJNR Am J Neuroradiol* 2002; **23**: 255–266.
113 Bigler ED, Blatter DD, Anderson CV, Johnson SC, Gale SD, Hopkins RO *et al.* Hippocampal volume in normal aging and traumatic brain injury. *AJNR Am J Neuroradiol* 1997; **18**: 11–23.
114 Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 1997; **277**: 376–380.
115 Di Stefano G, Bachevalier J, Levin HS, Song JX, Scheibel RS, Fletcher JM. Volume of focal brain lesions and hippocampal formation in relation to memory function after closed head injury in children. *J Neurol Neurosurg Psychiatry* 2000; **69**: 210–216.
116 Rauch SL, Kim H, Makris N, Cosgrove GR, Cassem EH, Savage CR *et al.* Volume reduction in the caudate nucleus following stereotactic placement of lesions in the anterior cingulate cortex in humans: a morphometric magnetic resonance imaging study. *J Neurosurg* 2000; **93**: 1019–1025.
117 Convit A, De Leon MJ, Tarshish C, De Santi S, Tsui W, Rusinek H *et al.* Specific hippocampal volume reductions in individuals at risk for Alzheimer's disease. *Neurobiol Aging* 1997; **18**: 131–138.
118 de Leon MJ, Convit A, George AE, Golomb J, de Santi S, Tarshish C *et al. In vivo* structural studies of the hippocampus in normal aging and in incipient Alzheimer's disease. *Ann NY Acad Sci* 1996; **777**: 1–13.
119 Fama R, Sullivan EV, Shear PK, Cahn-Weiner DA, Marsh L, Lim KO *et al.* Structural brain correlates of verbal and nonverbal fluency measures in Alzheimer's disease. *Neuropsychology* 2000; **14**: 29–40.
120 Freeborough PA, Fox NC, Kitney RI. Interactive algorithms for the segmentation and quantitation of 3-D MRI brain scans. *Comput Methods Programs Biomed* 1997; **53**: 15–25.
121 Jack Jr CR, Petersen RC, O'Brien PC, Tangalos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. *Neurology* 1992; **42**: 183–188.
122 Jack Jr CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ *et al.* Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology* 1998; **51**: 993–999.
123 Kidron D, Black SE, Stanchev P, Buck B, Szalai JP, Parker J *et al.* Quantitative MR volumetry in Alzheimer's disease. Topographic markers and the effects of sex and education. *Neurology* 1997; **49**: 1504–1512.
124 Laakso MP, Soininen H, Partanen K, Helkala EL, Hartikainen P, Vainio P *et al.* Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. *J Neural Transm Park Dis Dement Sect* 1995; **9**: 73–86.
125 O' Brien TJ, Ames D, Desmond P, Lichtenstein M, Binns D, Schweitzer I *et al.* Combined magnetic resonance imaging and single-photon emission tomography scanning in the discrimination of Alzheimer's disease from age-matched controls. *Int Psychogeriatr* 2001; **13**: 149–161.
126 Pantel J, Schroder J, Essig M, Popp D, Dech H, Knopp MV *et al.* Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J Affect Disord* 1997; **42**: 69–83.
127 Pitkanen A, Laakso M, Kalviainen R, Partanen K, Vainio P, Lehtovirta M *et al.* Severity of hippocampal atrophy correlates with the prolongation of MRI T2 relaxation time in temporal lobe epilepsy but not in Alzheimer's disease. *Neurology* 1996; **46**: 1724–1730.
128 Smith CD, Malcein M, Meurer K, Schmitt FA, Markesbery WR, Pettigrew LC. MRI temporal lobe volume measures and neuropsychologic function in Alzheimer's disease. *J Neuroimaging* 1999; **9**: 2–9.
129 Teipel SJ, Bayer W, Alexander GE, Bokde AL, Zebuhr Y, Teichberg D *et al.* Regional pattern of hippocampus and corpus callosum atrophy in Alzheimer's disease in relation to dementia severity: evidence for early neocortical degeneration. *Neurobiol Aging* 2003; **24**: 85–94.
130 Visser PJ, Scheltens P, Verhey FR, Schmand B, Launer LJ, Jolles J *et al.* Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. *J Neurol* 1999; **246**: 477–485.
131 de Toledo-Morrell L, Sullivan MP, Morrell F, Wilson RS, Bennett DA, Spencer S. Alzheimer's disease: *in vivo* detection of differential vulnerability of brain regions. *Neurobiol Aging* 1997; **18**: 463–468.
132 Lehericy S, Baulac M, Chiras J, Pierot L, Martin N, Pillon B *et al.* Amygdalohippocampal MR volume measurements in the early stages of Alzheimer disease. *AJNR Am J Neuroradiol* 1994; **15**: 929–937.
133 Sencakova D, Graff-Radford NR, Willis FB, Lucas JA, Parfitt F, Cha RH *et al.* Hippocampal atrophy correlates with clinical features of Alzheimer disease in African Americans. *Arch Neurol* 2001; **58**: 1593–1597.
134 Geroldi C, Laakso MP, DeCarli C, Beltramello A, Bianchetti A, Soininen H *et al.* Apolipoprotein E genotype and hippocampal asymmetry in Alzheimer's disease: a volumetric MRI study. *J Neurol Neurosurg Psychiatry* 2000; **68**: 93–96.
135 Hashimoto M, Yasuda M, Tanimukai S, Matsui M, Hirono N, Kazui H *et al.* Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. *Neurology* 2001; **57**: 1461–1466.
136 Lehtovirta M, Soininen H, Laakso MP, Partanen K, Helisalmi S, Mannermaa A *et al.* SPECT and MRI analysis in Alzheimer's disease: relation to apolipoprotein E epsilon 4 allele. *J Neurol Neurosurg Psychiatry* 1996; **60**: 644–649.
137 Bigler ED, Tate DF, Miller MJ, Rice SA, Hessel CD, Earl HD *et al.* Dementia, asymmetry of temporal lobe structures, and apolipoprotein E genotype: relationships to cerebral atrophy and neuropsychological impairment. *J Int Neuropsychol Soc* 2002; **8**: 925–933.
138 Wang L, Swank JS, Glick IE, Gado MH, Miller MI, Morris JC *et al.* Changes in hippocampal volume and shape across time

distinguish dementia of the Alzheimer type from healthy aging. *Neuroimage* 2003; **20**: 667–682.
139 Frisoni GB, Laakso MP, Beltramello A, Geroldi C, Bianchetti A, Soininen H *et al.* Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. *Neurology* 1999; **52**: 91–100.
140 Galton CJ, Patterson K, Graham K, Lambon-Ralph MA, Williams G, Antoun N *et al.* Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 2001; **57**: 216–225.
141 Hashimoto M, Kitagaki H, Imamura T, Hirono N, Shimomura T, Kazui H *et al.* Medial temporal and whole-brain atrophy in dementia with Lewy bodies: a volumetric MRI study. *Neurology* 1998; **51**: 357–362.
142 Laakso MP, Partanen K, Riekkinen P, Lehtovirta M, Helkala EL, Hallikainen M *et al.* Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: An MRI study. *Neurology* 1996; **46**: 678–681.
143 Maestu F, Arrazola J, Fernandez A, Simos PG, Amo C, Gil-Gregorio P *et al.* Do cognitive patterns of brain magnetic activity correlate with hippocampal atrophy in Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2003; **74**: 208–212.
144 Jack Jr CR, Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG *et al.* Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* 1997; **49**: 786–794.
145 Laakso MP, Soininen H, Partanen K, Lehtovirta M, Hallikainen M, Hanninen T *et al.* MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity, and analysis of the incorrectly classified subjects. *Neurobiol Aging* 1998; **19**: 23–31.
146 Wolf H, Grunwald M, Kruggel F, Riedel-Heller SG, Angerhofer S, Hojjatoleslami A *et al.* Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly. *Neurobiol Aging* 2001; **22**: 177–186.
147 De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish CY, Roche A *et al.* Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol Aging* 2001; **22**: 529–539.
148 El Fakhri G, Kijewski MF, Johnson KA, Syrkin G, Killiany RJ, Becker JA *et al.* MRI-guided SPECT perfusion measures and volumetric MRI in prodromal Alzheimer disease. *Arch Neurol* 2003; **60**: 1066–1072.
149 Morys J, Bobek-Billewicz B, Dziewiatkowski J, Bidzan L, Ussorowska D, Narklewicz O. Changes in the volume of temporal lobe structures related to Alzheimer's type dementia. *Folia Neuropathol* 2002; **40**: 47–56.
150 Dickerson BC, Goncharova I, Sullivan MP, Forchetti C, Wilson RS, Bennett DA *et al.* MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiol Aging* 2001; **22**: 747–754.
151 Du AT, Schuff N, Amend D, Laakso MP, Hsu YY, Jagust WJ *et al.* Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001; **71**: 441–447.
152 Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F *et al.* MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology* 2002; **58**: 1188–1196.
153 Pearlson GD, Harris GJ, Powers RE, Barta PE, Camargo EE, Chase GA *et al.* Quantitative changes in mesial temporal volume, regional cerebral blood flow, and cognition in Alzheimer's disease. *Arch Gen Psychiatry* 1992; **49**: 402–408.
154 Schuff N, Amend D, Ezekiel F, Steinman SK, Tanabe J, Norman D *et al.* Changes of hippocampal *N*-acetyl aspartate and volume in Alzheimer's disease. A proton MR spectroscopic imaging and MRI study. *Neurology* 1997; **49**: 1513–1521.
155 Karas GB, Burton EJ, Rombouts SA, van Schijndel RA, O'Brien JT, Scheltens P *et al.* A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. *Neuroimage* 2003; **18**: 895–907.
156 Laakso MP, Hallikainen M, Hanninen T, Partanen K, Soininen H. Diagnosis of Alzheimer's disease: MRI of the hippocampus *vs* delayed recall. *Neuropsychologia* 2003; **38**: 579–584.
157 Xu Y, Jack Jr CR, O'Brien PC, Kokmen E, Smith GE, Ivnik RJ *et al.* Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. *Neurology* 2000; **54**: 1760–1767.
158 Hampel H, Teipel SJ, Bayer W, Alexander GE, Schwarz R, Schapiro MB *et al.* Age transformation of combined hippocampus and amygdala volume improves diagnostic accuracy in Alzheimer's disease. *J Neurol Sci* 2002; **194**: 15–19.
159 Laakso MP, Lehtovirta M, Partanen K, Riekkinen PJ, Soininen H. Hippocampus in Alzheimer's disease: a 3-year follow-up MRI study. *Biol Psychiatry* 2000; **47**: 557–561.
160 Bobinski M, de Leon MJ, Wegiel J, Desanti S, Convit A, Saint Louis LA *et al.* The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. *Neuroscience* 2000; **95**: 721–725.
161 Deweer B, Lehericy S, Pillon B, Baulac M, Chiras J, Marsault C *et al.* Memory disorders in probable Alzheimer's disease: the role of hippocampal atrophy as shown with MRI. *J Neurol Neurosurg Psychiatry* 1995; **58**: 590–597.
162 Heun R, Mazanek M, Atzor KR, Tintera J, Gawehn J, Burkart M *et al.* Amygdala–hippocampal atrophy and memory performance in dementia of Alzheimer type. *Dement Geriatr Cogn Disord* 1997; **8**: 329–336.
163 Petersen RC, Jack Jr CR, Xu YC, Waring SC, O'Brien PC, Smith GE *et al.* Memory and MRI-based hippocampal volumes in aging and AD. *Neurology* 2000; **54**: 581–587.
164 Wilson RS, Sullivan M, de Toledo-Morrell L, Stebbins GT, Bennett DA, Morrell F. Association of memory and cognition in alzheimer's disease with volumetric estimates of temporal lobe structures. *Neuropsychology* 1996; **10**: 459–463.
165 Kohler S, Black SE, Sinden M, Szekely C, Kidron D, Parker JL *et al.* Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: an MR volumetry study in Alzheimer's disease. *Neuropsychologia* 1998; **36**: 901–914.
166 de Toledo-Morrell L, Dickerson B, Sullivan MP, Spanovic C, Wilson R, Bennett DA. Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. *Hippocampus* 2000; **10**: 136–142.
167 Mori E, Yoneda Y, Yamashita H, Hirono N, Ikeda M, Yamadori A. Medial temporal structures relate to memory impairment in Alzheimer's disease: an MRI volumetric study. *J Neurol Neurosurg Psychiatry* 2000; **63**: 214–221.
168 Mori E, Ikeda M, Hirono N, Kitagaki H, Imamura T, Shimomura T. Amygdalar volume and emotional memory in Alzheimer's disease. *Am J Psychiatry* 1999; **156**: 216–222.
169 Fox NC, Warrington EK, Freeborough PA, Hartikainen P, Kennedy AM, Stevens JM *et al.* Presymptomatic hippocampal atrophy in Alzheimer's disease. *A longitudinal MRI study. Brain* 1996; **119**(Part 6): 2001–2007.
170 Fox NC, Warrington EK, Stevens JM, Rossor MN. Atrophy of the hippocampal formation in early familial Alzheimer's disease. A longitudinal MRI study of at-risk members of a family with an amyloid precursor protein 717Val-Gly mutation. *Ann NY Acad Sci* 1996; **777**: 226–232.
171 Marquis S, Moore MM, Howieson DB, Sexton G, Payami H, Kaye JA *et al.* Independent predictors of cognitive decline in healthy elderly persons. *Arch Neurol* 2002; **59**: 601–606.
172 Mungas D, Reed BR, Jagust WJ, DeCarli C, Mack WJ, Kramer JH *et al.* Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. *Neurology* 2002; **59**: 867–873.
173 Schott JM, Fox NC, Frost C, Scahill RI, Janssen JC, Chan D *et al.* Assessing the onset of structural change in familial Alzheimer's disease. *Ann Neurol* 2003; **53**: 181–188.
174 Cohen RM, Small C, Lalonde F, Friz J, Sunderland T. Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. *Neurology* 2001; **57**: 2223–2228.
175 Soininen H, Partanen K, Pitkanen A, Hallikainen M, Hanninen T, Helisalmi S *et al.* Decreased hippocampal volume asymmetry on MRIs in nondemented elderly subjects carrying the apolipoprotein E epsilon 4 allele. *Neurology* 1995; **45**: 391–392.
176 Reiman EM, Uecker A, Caselli RJ, Lewis S, Bandy D, de Leon MJ *et al.* Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. *Ann Neurol* 1998; **44**: 288–291.
177 Jack Jr CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ *et al.* Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology* 2000; **55**: 484–489.

178 Jack Jr CR, Slomkowski M, Gracon S, Hoover TM, Felmlee JP, Stewart K *et al.* MRI as a biomarker of disease progression in a therapeutic trial of milameline for AD. *Neurology* 2003; **60**: 253–260.
179 Crum WR, Scahill RI, Fox NC. Automated hippocampal segmentation by regional fluid registration of serial MRI: validation and application in Alzheimer's disease. *Neuroimage* 2001; **13**: 847–855.
180 Gosche KM, Mortimer JA, Smith CD, Markesbery WR, Snowdon DA. An automated technique for measuring hippocampal volumes from MR imaging studies. *AJNR Am J Neuroradiol* 2001; **22**: 1686–1689.
181 Murphy C, Jernigan TL, Fennema-Notestine C. Left hippocampal volume loss in Alzheimer's disease is reflected in performance on odor identification: a structural MRI study. *J Int Neuropsychol Soc* 2003; **9**: 459–471.
182 Cardenas VA, Du AT, Hardin D, Ezekiel F, Weber P, Jagust WJ *et al.* Comparison of methods for measuring longitudinal brain change in cognitive impairment and dementia. *Neurobiol Aging* 2003; **24**: 537–544.
183 Grunwald M, Busse F, Hensel A, Kruggel F, Riedel-Heller S, Wolf H *et al.* Correlation between cortical theta activity and hippocampal volumes in health, mild cognitive impairment, and mild dementia. *J Clin Neurophysiol* 2001; **18**: 178–184.
184 Barber R, McKeith IG, Ballard C, Gholkar A, O'Brien JT. A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: magnetic resonance imaging volumetric study. *Dement Geriatr Cogn Disord* 2001; **12**: 198–205.
185 Fein G, Di Sclafani V, Tanabe J, Cardenas V, Weiner MW, Jagust WJ *et al.* Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. *Neurology* 2000; **55**: 1626–1635.
186 Du AT, Schuff N, Laakso MP, Zhu XP, Jagust WJ, Yaffe K *et al.* Effects of subcortical ischemic vascular dementia and AD on entorhinal cortex and hippocampus. *Neurology* 2002; **58**: 1635–1641.
187 Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol* 2000; **47**: 36–45.
188 Barber R, Ballard C, McKeith IG, Gholkar A, O'Brien JT. MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. *Neurology* 2000; **54**: 1304–1309.
189 Burton EJ, Karas G, Paling SM, Barber R, Williams ED, Ballard CG *et al.* Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. *Neuroimage* 2002; **17**: 618–630.
190 Bigler ED, Kerr B, Victoroff J, Tate DF, Breitner JC. White matter lesions, quantitative magnetic resonance imaging, and dementia. *Alzheimer Dis Assoc Disord* 2002; **16**: 161–170.
191 Simons JS, Verfaellie M, Galton CJ, Miller BL, Hodges JR, Graham KS. Recollection-based memory in frontotemporal dementia: implications for theories of long-term memory. *Brain* 2002; **125**: 2523–2536.
192 Bigler ED, Tate DF. Brain volume, intracranial volume, and dementia. *Invest Radiol* 2001; **36**: 539–546.
193 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001; **58**: 1985–1992.
194 Crook T, Bahar H, Sudilovsky A. Age-associated memory impairment: diagnostic criteria and treatment strategies. *Int J Neurol* 1987–1988; **21–22**: 73–82.
195 Convit A, de Leon MJ, Golomb J, George AE, Tarshish CY, Bobinski M *et al.* Hippocampal atrophy in early Alzheimer's disease: anatomic specificity and validation. *Psychiatr Q* 1993; **64**: 371–387.
196 Jack Jr CR, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ *et al.* Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999; **52**: 1397–1403.
197 Grundman M, Sencakova D, Jack Jr CR, Petersen RC, Kim HT, Schultz A *et al.* Brain MRI hippocampal volume and prediction of clinical status in a mild cognitive impairment trial. *J Mol Neurosci* 2002; **19**: 23–27, (Notes: CORPORATE NAME: Alzheimer's Disease Cooperative Study).
198 Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *J Neurol Neurosurg Psychiatry* 2002; **72**: 491–497.
199 Convit A, de Asis J, de Leon MJ, Tarshish CY, De Santi S, Rusinek H. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. *Neurobiol Aging* 2000; **21**: 19–26.
200 Chetelat G, Desgranges B, de la Sayette V, Viader F, Berkouk K, Landeau B *et al.* Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain* 2003; **126**: 1955–1967.
201 Bhatia S, Bookheimer SY, Gaillard WD, Theodore WH. Measurement of whole temporal lobe and hippocampus for MR volumetry: normative data. *Neurology* 1993; **43**: 2006–2010.
202 Convit A, de Leon MJ, Tarshish C, De Santi S, Kluger A, Rusinek H *et al.* Hippocampal volume losses in minimally impaired elderly. *Lancet* 1995; **345**: 266.
203 Convit A, de Leon MJ, Hoptman MJ, Tarshish C, De Santi S, Rusinek H. Age-related changes in brain: I. Magnetic resonance imaging measures of temporal lobe volumes in normal subjects. *Psychiatr Q* 1995; **66**: 343–355.
204 Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J *et al.* Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol Aging* 2001; **22**: 581–594.
205 Mu Q, Xie J, Wen Z, Weng Y, Shuyun Z. A quantitative MR study of the hippocampal formation, the amygdala, and the temporal horn of the lateral ventricle in healthy subjects 40 to 90 years of age. *AJNR Am J Neuroradiol* 1999; **20**: 207–211.
206 Mueller EA, Moore MM, Kerr DC, Sexton G, Camicioli RM, Howieson DB *et al.* Brain volume preserved in healthy elderly through the eleventh decade. *Neurology* 1998; **51**: 1555–1562.
207 Raz N, Gunning-Dixon FM, Head D, Dupuis JH, Acker JD. Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. *Neuropsychology* 1998; **12**: 95–114.
208 Tisserand DJ, Visser PJ, van Boxtel MP, Jolles J. The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. *Neurobiol Aging* 2000; **21**: 569–576.
209 Wolf OT, Convit A, de Leon MJ, Caraos C, Qadri SF. Basal hypothalamo-pituitary-adrenal axis activity and corticotropin feedback in young and older men: relationships to magnetic resonance imaging-derived hippocampus and cingulate gyrus volumes. *Neuroendocrinology* 2002; **75**: 241–249.
210 Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. *Neurobiol Aging* 1995; **16**: 591–606.
211 Kaye JA, Swihart T, Howieson D, Dame A, Moore MM, Karnos T *et al.* Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. *Neurology* 1997; **48**: 1297–1304.
212 Wu CC, Mungas D, Petkov CI, Eberling JL, Zrelak PA, Buonocore MH *et al.* Brain structure and cognition in a community sample of elderly Latinos. *Neurology* 2002; **59**: 383–391.
213 Golomb J, Kluger A, de Leon MJ, Ferris SH, Convit A, Mittelman MS *et al.* Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. *Learn Mem* 1994; **1**: 45–54.
214 Golomb J, de Leon MJ, George AE, Kluger A, Convit A, Rusinek H *et al.* Hippocampal atrophy correlates with severe cognitive impairment in elderly patients with suspected normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry* 1994; **57**: 590–593.
215 Murphy DG, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrini P *et al.* Sex differences in human brain morphometry, metabolism: an *in vivo* quantitative magnetic resonance imaging, positron emission tomography study on the effect of aging. *Arch Gen Psychiatry* 1996; **53**: 585–594.
216 den Heijer T, Vermeer SE, Clarke R, Oudkerk M, Koudstaal PJ, Hofman A *et al.* Homocysteine, brain atrophy on MRI of non-demented elderly. *Brain* 2003; **126**: 170–175.
217 Hackert VH, den Heijer T, Oudkerk M, Koudstaal PJ, Hofman A, Breteler MM. Hippocampal head size associated with verbal

memory performance in nondemented elderly. *Neuroimage* 2002; **17**: 1365–1372.
218 Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A *et al.* A prospective study of estrogen replacement therapy, the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 1997; **48**: 1517–1521.
219 Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B *et al.* Effect of oestrogen during menopause on risk, age at onset of Alzheimer's disease. *Lancet* 1996; **348**: 429–432.
220 Eberling JL, Wu C, Haan MN, Mungas D, Buonocore M, Jagust WJ. Preliminary evidence that estrogen protects against age-related hippocampal atrophy. *Neurobiol Aging* 2003; **24**: 725–732.
221 den Heijer T, Geerlings MI, Hofman A, de Jong FH, Launer LJ, Pols HA *et al.* Higher estrogen levels are not associated with larger hippocampi and better memory performance. *Arch Neurol* 2003; **60**: 213–220.
222 Haznedar MM, Buchsbaum MS, Wei TC, Hof PR, Cartwright C, Bienstock CA *et al.* Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. *Am J Psychiatry* 2000; **157**: 1994–2001.
223 Piven J, Bailey J, Ranson BJ, Arndt S. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. *J Autism Dev Disord* 1998; **28**: 105–110.
224 Aylward EH, Minshew NJ, Goldstein G, Honeycutt NA, Augustine AM, Yates KO *et al.* MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology* 1999; **53**: 2145–2150.
225 Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A *et al.* Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain* 2003; **126**: 1182–1192.
226 Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA *et al.* Brain structural abnormalities in young children with autism spectrum disorder. *Neurology* 2002; **59**: 184–192.
227 Raz N, Torres IJ, Briggs SD, Spencer WD, Thornton AE, Loken WJ *et al.* Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: evidence from MRI morphometry. *Neurology* 1995; **45**: 356–366.
228 Krasuski JS, Alexander GE, Horwitz B, Rapoport SI, Schapiro MB. Relation of medial temporal lobe volumes to age and memory function in nondemented adults with Down's syndrome: implications for the prodromal phase of Alzheimer's disease. *Am J Psychiatry* 2002; **159**: 74–81.
229 Pinter JD, Brown WE, Eliez S, Schmitt JE, Capone GT, Reiss AL. Amygdala and hippocampal volumes in children with Down syndrome: a high-resolution MRI study. *Neurology* 2001; **56**: 972–974.
230 Teipel SJ, Schapiro MB, Alexander GE, Krasuski JS, Horwitz B, Hoehne C *et al.* Relation of corpus callosum and hippocampal size to age in nondemented adults with Down's syndrome. *Am J Psychiatry* 2003; **160**: 1870–1878.
231 Pearlson GD, Breiter SN, Aylward EH, Warren AC, Grygorcewicz M, Frangou S *et al.* MRI brain changes in subjects with Down syndrome with and without dementia. *Dev Med Child Neurol* 1998; **40**: 326–334.
232 Aylward EH, Li Q, Honeycutt NA, Warren AC, Pulsifer MB, Barta PE *et al.* MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia. *Am J Psychiatry* 1999; **156**: 564–568.
233 Bogerts B, Lieberman JA, Ashtari M, Bilder RM, Degreef G, Lerner G *et al.* Hippocampus-amygdala volumes and psychopathology in chronic schizophrenia. *Biol Psychiatry* 1993; **33**: 236–246.
234 Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F. Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. *Arch Gen Psychiatry* 1992; **49**: 921–926.
235 Buchanan RW, Breier A, Kirkpatrick B, Elkashef A, Munson RC, Gellad F *et al.* Structural abnormalities in deficit and nondeficit schizophrenia. *Am J Psychiatry* 1993; **150**: 59–65.
236 Falkai P, Honer WG, Alfter D, Schneider-Axmann T, Bussfeld P, Cordes J *et al.* The temporal lobe in schizophrenia from uni- and multiply affected families. *Neurosci Lett* 2002; **325**: 25–28.
237 Flaum M, Swayze II VW, O'Leary DS, Yuh WT, Ehrhardt JC, Arndt SV *et al.* Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. *Am J Psychiatry* 1995; **152**: 704–714.
238 Fukuzako H, Fukazako T, Hashiguchi T, Hokazono Y, Takeuchi K, Hirakawa K *et al.* Reduction in hippocampal formation volume is caused mainly by its shortening in chronic schizophrenia: assessment by MRI. *Biol Psychiatry* 1996; **39**: 938–945.
239 Fukuzako H, Yamada K, Kodama S, Yonezawa T, Fukuzako T, Takenouchi K *et al.* Hippocampal volume asymmetry and age at illness onset in males with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 1997; **247**: 248–251.
240 Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI *et al.* Temporolimbic volume reductions in schizophrenia. *Arch Gen Psychiatry* 2000; **57**: 769–775.
241 Haller JW, Banerjee A, Christensen GE, Gado M, Joshi S, Miller MI *et al.* Three-dimensional hippocampal MR morphometry with high-dimensional transformation of a neuroanatomic atlas. *Radiology* 1997; **202**: 504–510.
242 Kwon JS, Shin YW, Kim CW, Kim YI, Youn T, Han MH *et al.* Similarity and disparity of obsessive–compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus–amygdala complex. *J Neurol Neurosurg Psychiatry* 2003; **74**: 962–964.
243 Rossi A, Stratta P, Mancini F, Gallucci M, Mattei P, Core L *et al.* Magnetic resonance imaging findings of amygdala-anterior hippocampus shrinkage in male patients with schizophrenia. *Psychiatry Res* 1994; **52**: 43–53.
244 Savas HA, Unal B, Erbagci H, Inaloz S, Herken H, Canan S *et al.* Hippocampal volume in schizophrenia and its relationship with risperidone treatment: a stereological study. *Neuropsychobiology* 2002; **46**: 61–66.
245 Suddath RL, Christison GW, Torrey EF, Casanova MF, Weinberger DR. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med* 1990; **322**: 789–794.
246 Velakoulis D, Stuart GW, Wood SJ, Smith DJ, Brewer WJ, Desmond P *et al.* Selective bilateral hippocampal volume loss in chronic schizophrenia. *Biol Psychiatry* 2001; **50**: 531–539.
247 Velakoulis D, Pantelis C, McGorry PD, Dudgeon P, Brewer W, Cook M *et al.* Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. *Arch Gen Psychiatry* 1999; **56**: 133–141.
248 Flaum M, O'Leary DS, Swayze II VW, Miller DD, Arndt S, Andreasen NC. Symptom dimensions and brain morphology in schizophrenia and related psychotic disorders. *J Psychiatr Res* 1995; **29**: 261–276.
249 Luchins DJ, Nettles KW, Goldman MB. Anterior medial temporal lobe volumes in polydipsic schizophrenic patients with and without hypo-osmolemia: a pilot study. *Biol Psychiatry* 1997; **42**: 767–770.
250 Baare WF, van Oel CJ, Hulshoff Pol HE, Schnack HG, Durston S, Sitskoorn MM *et al.* Volumes of brain structures in twins discordant for schizophrenia. *Arch Gen Psychiatry* 2001; **58**: 33–40.
251 Becker T, Elmer K, Schneider F, Schneider M, Grodd W, Bartels M *et al.* Confirmation of reduced temporal limbic structure volume on magnetic resonance imaging in male patients with schizophrenia. *Psychiatry Res* 1996; **67**: 135–143.
252 Narr K, Thompson P, Sharma T, Moussai J, Zoumalan C, Rayman J *et al.* Three-dimensional mapping of gyral shape and cortical surface asymmetries in schizophrenia: gender effects. *Am J Psychiatry* 2001; **158**: 244–255.
253 Anderson JE, Wible CG, McCarley RW, Jakab M, Kasai K, Shenton ME. An MRI study of temporal lobe abnormalities and negative symptoms in chronic schizophrenia. *Schizophr Res* 2002; **58**: 123–134.
254 Pegues MP, Rogers LJ, Amend D, Vinogradov S, Deicken RF. Anterior hippocampal volume reduction in male patients with schizophrenia. *Schizophr Res* 2003; **60**: 105–115.
255 Hulshoff Pol HE, Schnack HG, Mandl RC, van Haren NE, Koning H, Collins DL *et al.* Focal gray matter density changes in schizophrenia. *Arch Gen Psychiatry* 2001; **58**: 1118–1125.
256 Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG *et al.* Abnormalities of the left temporal lobe and thought

disorder in schizophrenia. A quantitative magnetic resonance imaging study. *N Engl J Med* 1992; **327**: 604–612.
257 Woodruff PW, Wright IC, Shuriquie N, Russouw H, Rushe T, Howard RJ *et al.* Structural brain abnormalities in male schizophrenics reflect fronto-temporal dissociation. *Psychol Med* 1997; **27**: 1257–1266.
258 Stefanis N, Frangou S, Yakeley J, Sharma T, O'Connell P, Morgan K *et al.* Hippocampal volume reduction in schizophrenia: effects of genetic risk and pregnancy and birth complications. *Biol Psychiatry* 1999; **46**: 697–702.
259 Bryant NL, Buchanan RW, Vladar K, Breier A, Rothman M. Gender differences in temporal lobe structures of patients with schizophrenia: a volumetric MRI study. *Am J Psychiatry* 1999; **156**: 603–609.
260 Colombo C, Abbruzzese M, Livian S, Scotti G, Locatelli M, Bonfanti A *et al.* Memory functions and temporal-limbic morphology in schizophrenia. *Psychiatry Res* 1993; **50**: 45–56.
261 Csernansky JG, Wang L, Jones D, Rastogi-Cruz D, Posener JA, Heydebrand G *et al.* Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. *Am J Psychiatry* 2002; **159**: 2000–2006.
262 Deicken RF, Pegues M, Amend D. Reduced hippocampal *N*-acetylaspartate without volume loss in schizophrenia. *Schizophr Res* 1999; **37**: 217–223.
263 Kegeles LS, Shungu DC, Anjilvel S, Chan S, Ellis SP, Xanthopoulos E *et al.* Hippocampal pathology in schizophrenia: magnetic resonance imaging and spectroscopy studies. *Psychiatry Res* 2000; **98**: 163–175.
264 Kelsoe Jr JR, Cadet JL, Pickar D, Weinberger DR. Quantitative neuroanatomy in schizophrenia. A controlled magnetic resonance imaging study. *Arch Gen Psychiatry* 1988; **45**: 533–541.
265 Rajarethinam R, DeQuardo JR, Miedler J, Arndt S, Kirbat R, Brunberg JA *et al.* Hippocampus and amygdala in schizophrenia: assessment of the relationship of neuroanatomy to psychopathology. *Psychiatry Res* 2001; **108**: 79–87.
266 Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A *et al.* Volumetric measure of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. *Arch Gen Psychiatry* 2000; **57**: 471–480.
267 Swayze II VW, Andreasen NC, Alliger RJ, Yuh WT, Ehrhardt JC. Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. *Biol Psychiatry* 1992; **31**: 221–240.
268 Torres IJ, Flashman LA, O'Leary DS, Swayze II V, Andreasen NC. Lack of an association between delayed memory and hippocampal and temporal lobe size in patients with schizophrenia and healthy controls. *Biol Psychiatry* 1997; **42**: 1087–1096.
269 Wright IC, McGuire PK, Poline JB, Travere JM, Murray RM, Frith CD *et al.* A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *Neuroimage* 1995; **2**: 244–252.
270 Zipursky RB, Marsh L, Lim KO, DeMent S, Shear PK, Sullivan EV *et al.* Volumetric MRI assessment of temporal lobe structures in schizophrenia. *Biol Psychiatry* 1994; **35**: 501–516.
271 Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. *Arch Gen Psychiatry* 1998; **55**: 433–440.
272 Csernansky JG, Joshi S, Wang L, Haller JW, Gado M, Miller JP *et al.* Hippocampal morphometry in schizophrenia by high dimensional brain mapping. *Proc Natl Acad Sci USA* 1998; **95**: 11406–11411.
273 Shenton ME, Gerig G, McCarley RW, Szekely G, Kikinis R. Amygdala-hippocampal shape differences in schizophrenia: the application of 3D shape models to volumetric MR data. *Psychiatry Res* 2002; **115**: 15–35.
274 Wang L, Joshi SC, Miller MI, Csernansky JG. Statistical analysis of hippocampal asymmetry in schizophrenia. *Neuroimage* 2001; **14**: 531–545.
275 DeLisi LE, Tew W, Xie S, Hoff AL, Sakuma M, Kushner M *et al.* A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. *Biol Psychiatry* 1995; **38**: 349–360.
276 Arango C, Breier A, McMahon R, Carpenter Jr WT, Buchanan RW. The relationship of clozapine and haloperidol treatment response to prefrontal, hippocampal, and caudate brain volumes. *Am J Psychiatry* 2003; **160**: 1421–1427.
277 Bogerts B, Ashtari M, Degreef G, Alvir JM, Bilder RM, Lieberman JA. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatry Res* 1990; **35**: 1–13.
278 Kubicki M, Shenton ME, Salisbury DF, Hirayasu Y, Kasai K, Kikinis R *et al.* Voxel-based morphometric analysis of gray matter in first episode schizophrenia. *Neuroimage* 2002; **17**: 1711–1719.
279 Hirayasu Y, Shenton ME, Salisbury DF, Dickey CC, Fischer IA, Mazzoni P *et al.* Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. *Am J Psychiatry* 1998; **155**: 1384–1391.
280 Sumich A, Chitnis XA, Fannon DG, O'Ceallaigh S, Doku VC, Falrowicz A *et al.* Temporal lobe abnormalities in first-episode psychosis. *Am J Psychiatry* 2002; **159**: 1232–1235.
281 Whitworth AB, Honeder M, Kremser C, Kemmler G, Felber S, Hausmann A *et al.* Hippocampal volume reduction in male schizophrenic patients. *Schizophr Res* 1998; **31**: 73–81.
282 Bilder RM, Bogerts B, Ashtari M, Wu H, Alvir JM, Jody D *et al.* Anterior hippocampal volume reductions predict frontal lobe dysfunction in first episode schizophrenia. *Schizophr Res* 1995; **17**: 47–58.
283 Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D *et al.* Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry* 2001; **49**: 487–499.
284 Szeszko PR, Goldberg E, Gunduz-Bruce H, Ashtari M, Robinson D, Malhotra AK *et al.* Smaller anterior hippocampal formation volume in antipsychotic-naive patients with first-episode schizophrenia. *Am J Psychiatry* 2003; **160**: 2190–2197.
285 Cahn W, Pol HE, Bongers M, Schnack HG, Mandl RC, Van Haren NE *et al.* Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. *Br J Psychiatry Suppl* 2002; **43**: s66–s72.
286 Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. *Neuroimage* 2002; **17**: 880–889.
287 Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Lee CU, Ciszewski AA *et al.* Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. *Am J Psychiatry* 2003; **160**: 156–164.
288 Laakso MP, Tiihonen J, Syvalahti E, Vilkman H, Laakso A, Alakare B *et al.* A morphometric MRI study of the hippocampus in first-episode, neuroleptic-naive schizophrenia. *Schizophr Res* 2001; **50**: 3–7.
289 Niemann K, Hammers A, Coenen VA, Thron A, Klosterkotter J. Evidence of a smaller left hippocampus and left temporal horn in both patients with first episode schizophrenia and normal control subjects. *Psychiatry Res* 2000; **99**: 93–110.
290 Wood SJ, Velakoulis D, Smith DJ, Bond D, Stuart GW, McGorry PD *et al.* A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. *Schizophr Res* 2001; **52**: 37–46.
291 Szeszko PR, Strous RD, Goldman RS, Ashtari M, Knuth KH, Lieberman JA *et al.* Neuropsychological correlates of hippocampal volumes in patients experiencing a first episode of schizophrenia. *Am J Psychiatry* 2002; **159**: 217–226.
292 Jacobsen LK, Giedd JN, Castellanos FX, Vaituzis AC, Hamburger SD, Kumra S *et al.* Progressive reduction of temporal lobe structures in childhood-onset schizophrenia. *Am J Psychiatry* 1998; **155**: 678–685.
293 Giedd JN, Jeffries NO, Blumenthal J, Castellanos FX, Vaituzis AC, Fernandez T *et al.* Childhood-onset schizophrenia: progressive brain changes during adolescence. *Biol Psychiatry* 1999; **46**: 892–898.
294 Levitt JG, Blanton RE, Caplan R, Asarnow R, Guthrie D, Toga AW *et al.* Medial temporal lobe in childhood-onset schizophrenia. *Psychiatry Res* 2001; **108**: 17–27.

295 Matsumoto H, Simmons A, Williams S, Pipe R, Murray R, Frangou S. Structural magnetic imaging of the hippocampus in early onset schizophrenia. *Biol Psychiatry* 2001; **49**: 824–831.
296 Jacobsen LK, Giedd JN, Vaituzis AC, Hamburger SD, Rajapakse JC, Frazier JA *et al.* Temporal lobe morphology in childhood-onset schizophrenia. *Am J Psychiatry* 1996; **153**: 355–361.
297 Barta PE, Powers RE, Aylward EH, Chase GA, Harris GJ, Rabins PV *et al.* Quantitative MRI volume changes in late onset schizophrenia and Alzheimer's disease compared to normal controls. *Psychiatry Res* 1997; **68**: 65–75.
298 Keshavan MS, Dick E, Mankowski I, Harenski K, Montrose DM, Diwadkar V *et al.* Decreased left amygdala and hippocampal volumes in young offspring at risk for schizophrenia. *Schizophr Res* 2002; **58**: 173–183.
299 Phillips LJ, Velakoulis D, Pantelis C, Wood S, Yuen HP, Yung AR *et al.* Non-reduction in hippocampal volume is associated with higher risk of psychosis. *Schizophr Res* 2002; **58**: 145–158.
300 Keshavan MS, Montrose DM, Pierri JN, Dick EL, Rosenberg D, Talagala L *et al.* Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: preliminary studies. *Prog Neuropsychopharmacol Biol Psychiatry* 1997; **21**: 1285–1295.
301 Lawrie SM, Whalley H, Kestelman JN, Abukmeil SS, Byrne M, Hodges A *et al.* Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet* 1999; **353**: 30–33.
302 Tepest R, Wang L, Miller MI, Falkai P, Csernansky JG. Hippocampal deformities in the unaffected siblings of schizophrenia subjects. *Biol Psychiatry* 2003; **54**: 1234–1240.
303 Coffey CE, Wilkinson WE, Weiner RD, Parashos IA, Djang WT, Webb MC *et al.* Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. *Arch Gen Psychiatry* 1993; **50**: 7–16.
304 Axelson DA, Doraiswamy PM, McDonald WM, Boyko OB, Tupler LA, Patterson LJ *et al.* Hypercortisolemia and hippocampal changes in depression. *Psychiatry Res* 1993; **47**: 163–173.
305 Frodl T, Meisenzahl EM, Zetzsche T, Born C, Groll C, Jager M *et al.* Hippocampal changes in patients with a first episode of major depression. *Am J Psychiatry* 2002; **159**: 1112–1118.
306 Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999; **19**: 5034–5043.
307 Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 1996; **93**: 3908–3913.
308 MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT *et al.* Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc Natl Acad Sci USA* 2003; **100**: 1387–1392.
309 Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *Am J Psychiatry* 2000; **157**: 115–118.
310 Mervaala E, Fohr J, Kononen M, Valkonen-Korhonen M, Vainio P, Partanen K *et al.* Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychol Med* 2000; **30**: 117–125.
311 Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br J Psychiatry* 1998; **172**: 527–532.
312 Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM *et al.* Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. *Biol Psychiatry* 2000; **47**: 1087–1090.
313 von Gunten A, Fox NC, Cipolotti L, Ron MA. A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. *J Neuropsychiatry Clin Neurosci* 2000; **12**: 493–498.
314 Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R *et al.* Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 2002; **159**: 2072–2080.
315 Posener JA, Wang L, Price JL, Gado MH, Province MA, Miller MI *et al.* High-dimensional mapping of the hippocampus in depression. *Am J Psychiatry* 2003; **160**: 83–89.
316 Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *Am J Psychiatry* 2003; **160**: 1516–1518.
317 Kim DK, Kim BL, Sohn SE, Lim SW, Na DG, Paik CH *et al.* Candidate neuroanatomic substrates of psychosis in old-aged depression. *Prog Neuropsychopharmacol Biol Psychiatry* 1999; **23**: 793–807.
318 Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF *et al.* Hippocampal volume in geriatric depression. *Biol Psychiatry* 2000; **48**: 301–309.
319 Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds III CF, Becker JT. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. *Am J Psychiatry* 2002; **159**: 1424–1427.
320 Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC. Hippocampal volume and antidepressant response in geriatric depression. *Int J Geriatr Psychiatry* 2002; **17**: 519–525.
321 Steffens DC, Payne ME, Greenberg DL, Byrum CE, Welsh-Bohmer KA, Wagner HR *et al.* Hippocampal volume and incident dementia in geriatric depression. *Am J Geriatr Psychiatry* 2002; **10**: 62–71.
322 MacMillan S, Szeszko PR, Moore GJ, Madden R, Lorch E, Ivey J *et al.* Increased amygdala: hippocampal volume ratios associated with severity of anxiety in pediatric major depression. *J Child Adolesc Psychopharmacol* 2003; **13**: 65–73.
323 MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. *BMC Med* 2004; **2**: 2.
324 Altshuler LL, Bartzokis G, Grieder T, Curran J, Mintz J. Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study demonstrating neuroanatomic specificity. *Arch Gen Psychiatry* 1998; **55**: 663–664.
325 Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC *et al.* Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. *Arch Gen Psychiatry* 2003; **60**: 1201–1208.
326 Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM *et al.* Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Arch Gen Psychiatry* 1999; **56**: 254–260.
327 Hauser P, Matochik J, Altshuler LL, Denicoff KD, Conrad A, Li X *et al.* MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. *J Affect Disord* 2000; **60**: 25–32.
328 Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J *et al.* Ventricular and periventricular structural volumes in first-versus multiple-episode bipolar disorder. *Am J Psychiatry* 2002; **159**: 1841–1847.
329 Ali SO, Denicoff KD, Altshuler LL, Hauser P, Li X, Conrad AJ *et al.* Relationship between prior course of illness and neuroanatomic structures in bipolar disorder: a preliminary study. *Neuropsychiatry Neuropsychol Behav Neurol* 2001; **14**: 227–232.
330 Ali SO, Denicoff KD, Altshuler LL, Hauser P, Li X, Conrad AJ *et al.* A preliminary study of the relation of neuropsychological performance to neuroanatomic structures in bipolar disorder. *Neuropsychiatry Neuropsychol Behav Neurol* 2000; **13**: 20–28.
331 Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM *et al.* MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 1995; **152**: 973–981.
332 Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW *et al.* Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry* 1996; **40**: 1091–1099.
333 Villarreal G, Hamilton DA, Petropoulos H, Driscoll I, Rowland LM, Griego JA *et al.* Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. *Biol Psychiatry* 2002; **52**: 119–125.
334 Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C *et al.* Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse–a preliminary report. *Biol Psychiatry* 1997; **41**: 23–32.

335 Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 1997; **27**: 951–959.
336 Hedges DW, Allen S, Tate DF, Thatcher GW, Miller MJ, Rice SA *et al.* Reduced hippocampal volume in alcohol and substance naive Vietnam combat veterans with posttraumatic stress disorder. *Cogn Behav Neurol* 2003; **16**: 219–224.
337 Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP *et al.* Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 2002; **5**: 1242–1247.
338 Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK *et al.* Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *Am J Psychiatry* 2001; **158**: 1248–1251.
339 Fennema-Notestine C, Stein MB, Kennedy CM, Archibald SL, Jernigan TL. Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biol Psychiatry* 2002; **52**: 1089–1101.
340 Schuff N, Neylan TC, Lenoci MA, Du AT, Weiss DS, Marmar CR *et al.* Decreased hippocampal N-acetylaspartate in the absence of atrophy in posttraumatic stress disorder. *Biol Psychiatry* 2001; **50**: 952–959.
341 Neylan TC, Schuff N, Lenoci M, Yehuda R, Weiner MW, Marmar CR. Cortisol levels are positively correlated with hippocampal N-acetylaspartate. *Biol Psychiatry* 2003; **54**: 1118–1121.
342 Agartz I, Momenan R, Rawlings RR, Kerich MJ, Hommer DW. Hippocampal volume in patients with alcohol dependence. *Arch Gen Psychiatry* 1999; **56**: 356–363.
343 Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A *et al.* MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* 2003; **160**: 924–932.
344 Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry* 2003; **54**: 693–702.
345 Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, Abe O *et al.* Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proc Natl Acad Sci USA* 2003; **100**: 9039–9043.
346 Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD *et al.* Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry* 2001; **50**: 943–951.
347 De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J *et al.* Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry* 2002; **52**: 1066–1078.
348 De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry* 2001; **50**: 305–309.
349 De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM *et al.* A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. *Biol Psychiatry* 1999; **45**: 1271–1284.
350 Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Anterior hippocampal volume deficits in nonamnesic, aging chronic alcoholics. *Alcohol Clin Exp Res* 1995; **19**: 110–122.
351 Beresford T, Arciniegas D, Rojas D, Sheeder J, Teale P, Aasal R *et al.* Hippocampal to pituitary volume ratio: a specific measure of reciprocal neuroendocrine alterations in alcohol dependence. *J Stud Alcohol* 1999; **60**: 586–588.
352 Laakso MP, Vaurio O, Savolainen L, Repo E, Soininen H, Aronen HJ *et al.* A volumetric MRI study of the hippocampus in type 1 and 2 alcoholism. *Behav Brain Res* 2000; **109**: 177–186.
353 De Bellis MD, Clark DB, Beers SR, Soloff PH, Boring AM, Hall J *et al.* Hippocampal volume in adolescent-onset alcohol use disorders. *Am J Psychiatry* 2000; **157**: 737–744.
354 Bleich S, Bandelow B, Javaheripour K, Muller A, Degner D, Wilhelm J *et al.* Hyperhomocysteinemia as a new risk factor for brain shrinkage in patients with alcoholism. *Neurosci Lett* 2003; **335**: 179–182.
355 Bleich S, Sperling W, Degner D, Graesel E, Bleich K, Wilhelm J *et al.* Lack of association between hippocampal volume reduction and first-onset alcohol withdrawal seizure. *A volumetric MRI study. Alcohol Alcohol* 2003; **38**: 40–44.
356 Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Relationship between alcohol withdrawal seizures and temporal lobe white matter volume deficits. *Alcohol Clin Exp Res* 1996; **20**: 348–354.
357 Di Sclafani V, Truran DL. Abstinent chronic crack-cocaine and crack-cocaine/alcohol abusers evidence normal hippocampal volumes on MRI despite persistent cognitive impairments. *Addiction Biol* 1998; **3**: 261–271.
358 Honeycutt NA, Smith CD. Hippocampal volume measurements using magnetic resonance imaging in normal young adults. *J Neuroimaging* 1995; **5**: 95–100.
359 Pruessner JC, Li LM, Serles W, Pruessner M, Collins DL, Kabani N *et al.* Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. *Cereb Cortex* 2000; **10**: 433–442.
360 Mackay CE, Roberts N, Mayes AR, Downes JJ, Foster JK, Mann D. An exploratory study of the relationship between face recognition memory and the volume of medial temporal lobe structures in healthy young males. *Behav Neurol* 1998; **11**: 3–20.
361 Giedd JN, Vaituzis AC, Hamburger SD, Lange N, Rajapakse JC, Kaysen D *et al.* Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4-18 years. *J Comp Neurol* 1996; **366**: 223–230.
362 Szabo CA, Xiong J, Lancaster JL, Rainey L, Fox P. Amygdalar and hippocampal volumetry in control participants: differences regarding handedness. *AJNR Am J Neuroradiol* 2001; **22**: 1342–1345.
363 Obenaus A, Yong-Hing CJ, Tong KA, Sarty GE. A reliable method for measurement and normalization of pediatric hippocampal volumes. *Pediatr Res* 2001; **50**: 124–132.
364 Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL. Sexual dimorphism of the developing human brain. *Prog Neuropsychopharmacol Biol Psychiatry* 1997; **21**: 1185–1201.
365 Utsunomiya H, Takano K, Okazaki M, Mitsudome A. Development of the temporal lobe in infants and children: analysis by MR-based volumetry. *AJNR Am J Neuroradiol* 1999; **20**: 717–723.
366 Pfluger T, Weil S, Weis S, Vollmar C, Heiss D, Egger J *et al.* Normative volumetric data of the developing hippocampus in children based on magnetic resonance imaging. *Epilepsia* 1999; **40**: 414–423.
367 Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD *et al.* Selective aging of the human cerebral cortex observed *in vivo*: differential vulnerability of the prefrontal gray matter. *Cereb Cortex* 1997; **7**: 268–282.
368 Filipek PA, Richelme C, Kennedy DN, Caviness Jr VS. The young adult human brain: an MRI-based morphometric analysis. *Cereb Cortex* 1994; **4**: 344–360.
369 Caviness Jr VS, Kennedy DN, Richelme C, Rademacher J, Filipek PA. The human brain age 7-11 years: a volumetric analysis based on magnetic resonance images. *Cereb Cortex* 1996; **6**: 726–736.
370 Gur RC, Gunning-Dixon F, Bilker WB, Gur RE. Sex differences in temporo-limbic and frontal brain volumes of healthy adults. *Cereb Cortex* 2002; **12**: 998–1003.
371 Pruessner JC, Collins DL, Pruessner M, Evans AC. Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. *J Neurosci* 2001; **21**: 194–200.
372 Liu RS, Lemieux L, Bell GS, Sisodiya SM, Shorvon SD, Sander JW *et al.* A longitudinal study of brain morphometrics using quantitative magnetic resonance imaging and difference image analysis. *Neuroimage* 2003; **20**: 22–33.
373 Andreasen NC, Flaum M, Swayze II V, O'Leary DS, Alliger R, Cohen G *et al.* Intelligence and brain structure in normal individuals. *Am J Psychiatry* 1993; **150**: 130–134.
374 Foster JK, Meikle A, Goodson G, Mayes AR, Howard M, Sunram SI *et al.* The hippocampus and delayed recall: bigger is not necessarily better? *Memory* 1999; **7**: 715–732.
375 Chantome M, Perruchet P, Hasboun D, Dormont D, Sahel M, Sourour N *et al.* Is there a negative correlation between explicit

memory and hippocampal volume? *Neuroimage* 1999; **10**: 589–595.
376 Raz N, Williamson A, Gunning-Dixon F, Head D, Acker JD. Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. *Microsc Res Tech* 2000; **51**: 85–93.
377 Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS *et al.* Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci USA* 2000; **97**: 4398–4403.
378 Maguire EA, Spiers HJ, Good CD, Hartley T, Frackowiak RS, Burgess N. Navigation expertise and the human hippocampus: a structural brain imaging analysis. *Hippocampus* 2003; **13**: 250–259.
379 Bartzokis G, Mintz J, Marx P, Osborn D, Gutkind D, Chiang F *et al.* Reliability of *in vivo* volume measures of hippocampus and other brain structures using MRI. *Magn Reson Imaging* 1993; **11**: 993–1006.
380 Bilir E, Craven W, Hugg J, Gilliam F, Martin R, Faught E *et al.* Volumetric MRI of the limbic system: anatomic determinants. *Neuroradiology* 1998; **40**: 138–144.
381 Honeycutt NA, Smith PD, Aylward E, Li Q, Chan M, Barta PE *et al.* Mesial temporal lobe measurements on magnetic resonance imaging scans. *Psychiatry Res* 1998; **83**: 85–94.
382 Lemieux L, Liu RS, Duncan JS. Hippocampal and cerebellar volumetry in serially acquired MRI volume scans. *Magn Reson Imaging* 2000; **18**: 1027–1033.
383 Pantel J, O'Leary DS, Cretsinger K, Bockholt HJ, Keefe H, Magnotta VA *et al.* A new method for the *in vivo* volumetric measurement of the human hippocampus with high neuroanatomical accuracy. *Hippocampus* 2000; **10**: 752–758.
384 MacFall JR, Byrum CE, Parashos I, Early B, Charles HC, Chittilla V *et al.* Relative accuracy and reproducibility of regional MRI brain volumes for point-counting methods. *Psychiatry Res* 1994; **55**: 167–177.
385 Ashton EA, Berg MJ, Parker KJ, Weisberg J, Chen CW, Ketonen L. Segmentation and feature extraction techniques, with applications to MRI head studies. *Magn Reson Med* 1995; **33**: 670–677.
386 Hsu YY, Schuff N, Du AT, Mark K, Zhu X, Hardin D *et al.* Comparison of automated and manual MRI volumetry of hippocampus in normal aging and dementia. *J Magn Reson Imaging* 2002; **16**: 305–310.
387 Shen D, Moffat S, Resnick SM, Davatzikos C. Measuring size and shape of the hippocampus in MR images using a deformable shape model. *Neuroimage* 2002; **15**: 422–434.
388 Briellmann RS, Syngeniotis A, Jackson GD. Comparison of hippocampal volumetry at 1.5 tesla and at 3 tesla. *Epilepsia* 2001; **42**: 1021–1024.
389 Levy-Reiss I, Gonzalez-Atavales J, King-Stephens D, French JA, Baltuch G, Bagley L, Detre JA. High Resolution Imaging at 4 Tesla for Hippocampal Volumetry in Temporal Lobe Epilepsy. *Proc Intl Soc Magn Reson Med* 2000; **8**: 15.
390 Hasboun D, Chantome M, Zouaoui A, Sahel M, Deladoeuille M, Sourour N *et al.* MR determination of hippocampal volume: comparison of three methods. *AJNR Am J Neuroradiol* 1996; **17**: 1091–1098.
391 Bartzokis G, Altshuler LL, Greider T, Curran J, Keen B, Dixon WJ. Reliability of medial temporal lobe volume measurements using reformatted 3D images. *Psychiatry Res* 1998; **82**: 11–24.
392 Laakso MP, Juottonen K, Partanen K, Vainio P, Soininen H. MRI volumetry of the hippocampus: the effect of slice thickness on volume formation. *Magn Reson Imaging* 1997; **15**: 263–265.
393 Chee MW, Low S, Tan JS, Lim W, Wong J. Hippocampal volumetry with magnetic resonance imaging: a cost-effective validated solution. *Epilepsia* 1997; **38**: 461–465.
394 Trenerry MR, Westerveld M, Meador KJ. MRI hippocampal volume and neuropsychology in epilepsy surgery. *Magn Reson Imaging* 1995; **13**: 1125–1132.
395 Duncan JS. MRI studies. Do seizures damage the brain? *Prog Brain Res* 2002; **135**: 253–261.
396 Whalley HC, Kestelman JN, Rimmington JE, Kelso A, Abukmeil SS, Best JJ *et al.* Methodological issues in volumetric magnetic resonance imaging of the brain in the Edinburgh High Risk Project. *Psychiatry Res* 1999; **91**: 31–44.
397 Bertolino A, Nawroz S, Mattay VS, Barnett AS, Duyn JH, Moonen CT *et al.* Regionally specific pattern of neurochemical pathology in schizophrenia as assessed by multislice proton magnetic resonance spectroscopic imaging. *Am J Psychiatry* 1996; **153**: 1554–1563.
398 Nasrallah HA, Skinner TE, Schmalbrock P, Robitaille PM. Proton magnetic resonance spectroscopy (1H MRS) of the hippocampal formation in schizophrenia: a pilot study. *Br J Psychiatry* 1994; **165**: 481–485.
399 Callicott JH, Egan MF, Bertolino A, Mattay VS, Langheim FJ, Frank JA *et al.* Hippocampal *N*-acetyl aspartate in unaffected siblings of patients with schizophrenia: a possible intermediate neurobiological phenotype. *Biol Psychiatry* 1998; **44**: 941–950.
400 Church SM, Cotter D, Bramon E, Murray RM. Does schizophrenia result from developmental or degenerative processes? *J Neural Transm Suppl* 2002; 129–147.
401 Lieberman JA. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biol Psychiatry* 1999; **46**: 729–739.
402 Weinberger DR. Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry* 1999; **45**: 395–402.
403 Lipska BK, Weinberger DR. A neurodevelopmental model of schizophrenia: neonatal disconnection of the hippocampus. *Neurotox Res* 2002; **4**: 469–475.
404 Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB *et al.* Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* 2003; **362**: 798–805.
405 Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 2000; **57**: 925–935.
406 Sapolsky RM. Why stress is bad for your brain. *Science* 1996; **273**: 749–750.
407 Yehuda R. Are glucocortoids responsible for putative hippocampal damage in PTSD? How and when to decide. *Hippocampus* 2001; **11**: 85–89; discussion 82–84.
408 Bremner JD. Hypotheses and controversies related to effects of stress on the hippocampus: an argument for stress-induced damage to the hippocampus in patients with posttraumatic stress disorder. *Hippocampus* 2001; **11**: 75–81; discussion 82–84.
409 Elzinga BM, Schmahl CG, Vermetten E, van Dyck R, Bremner JD. Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. *Neuropsychopharmacology* 2003; **28**: 1656–1665.
410 Jacobs BL, Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry* 2000; **5**: 262–269.
411 Kempermann G, Kronenberg G. Depressed new neurons—adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. *Biol Psychiatry* 2003; **54**: 499–503.
412 Schmahl CG, Vermetten E, Elzinga BM, Douglas Bremner J. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Res* 2003; **122**: 193–198.
413 Abernethy LJ, Palaniappan M, Cooke RW. Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight. *Arch Dis Child* 2002; **87**: 279–283.
414 Murphy DG, DeCarli C, Daly E, Haxby JV, Allen G, White BJ *et al.* X-chromosome effects on female brain: a magnetic resonance imaging study of Turner's syndrome. *Lancet* 1993; **342**: 1197–1200.
415 Reiss AL, Lee J, Freund L. Neuroanatomy of fragile X syndrome: the temporal lobe. *Neurology* 1994; **44**: 1317–1324.
416 Fujioka M, Nishio K, Miyamoto S, Hiramatsu KI, Sakaki T, Okuchi K *et al.* Hippocampal damage in the human brain after cardiac arrest. *Cerebrovasc Dis* 2000; **10**: 2–7.
417 Braak H, Del Tredici K, Bohl J, Bratzke H, Braak E. Pathological changes in the parahippocampal region in select non-Alzheimer's dementias. *Ann NY Acad Sci* 2000; **911**: 221–239.
418 Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A *et al.* Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Arch Gen Psychiatry* 2000; **57**: 1115–1122.
419 Tebartz van Elst L, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L *et al.* Frontolimbic brain abnormalities in patients

with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biol Psychiatry* 2003; **54**: 163–171.
420 Szabo CA, Wyllie E, Siavalas EL, Najm I, Ruggieri P, Kotagal P *et al.* Hippocampal volumetry in children 6 years or younger: assessment of children with and without complex febrile seizures. *Epilepsy Res* 1999; **33**: 1–9.
421 Tarkka R, Paakko E, Pyhtinen J, Uhari M, Rantala H. Febrile seizures and mesial temporal sclerosis: No association in a long-term follow-up study. *Neurology* 2003; **60**: 215–218.
422 Yoneda Y, Mori E, Yamashita H, Yamadori A. MRI volumetry of medial temporal lobe structures in amnesia following herpes simplex encephalitis. *Eur Neurol* 1994; **34**: 243–252.
423 Caparros-Lefebvre D Girard-Buttaz I Reboul S Lebert F Cabaret M Verier A *et al*. Cognitive and psychiatric impairment in herpes simplex virus encephalitis suggest involvement of the amygdalo-frontal pathways. *J Neurol* 1996; **243**: 248–256.
424 Colchester A, Kingsley D, Lasserson D, Kendall B, Bello F, Rush C *et al.* Structural MRI volumetric analysis in patients with organic amnesia, 1: methods and comparative findings across diagnostic groups. *J Neurol Neurosurg Psychiatry* 2001; **71**: 13–22.
425 Visser PJ, Krabbendam L, Verhey FR, Hofman PA, Verhoeven WM, Tuinier S *et al.* Brain correlates of memory dysfunction in alcoholic Korsakoff's syndrome. *J Neurol Neurosurg Psychiatry* 1999; **67**: 774–778.
426 Sullivan EV, Marsh L. Hippocampal volume deficits in alcoholic Korsakoff's syndrome. *Neurology* 2003; **61**: 1716–1719.
427 Jenike MA, Breiter HC, Baer L, Kennedy DN, Savage CR, Olivares MJ *et al.* Cerebral structural abnormalities in obsessive–compulsive disorder. A quantitative morphometric magnetic resonance imaging study. *Arch Gen Psychiatry* 1996; **53**: 625–632.
428 Szeszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M *et al.* Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Arch Gen Psychiatry* 1999; **56**: 913–919.
429 Kopelman MD, Lasserson D, Kingsley D, Bello F, Rush C, Stanhope N *et al.* Structural MRI volumetric analysis in patients with organic amnesia, 2: correlations with anterograde memory and executive tests in 40 patients. *J Neurol Neurosurg Psychiatry* 2001; **71**: 23–28.
430 Isaacs EB, Vargha-Khadem F, Watkins KE, Lucas A, Mishkin M, Gadian DG. Developmental amnesia and its relationship to degree of hippocampal atrophy. *Proc Natl Acad Sci USA* 2003; **100**: 13060–13063.
431 Grubb NR, Fox KA, Smith K, Best J, Blane A, Ebmeier KP *et al.* Memory impairment in out-of-hospital cardiac arrest survivors is associated with global reduction in brain volume, not focal hippocampal injury. *Stroke* 2000; **31**: 1509–1514.
432 Starkman MN, Gebarski SS, Berent S, Schteingart DE. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biol Psychiatry* 1992; **32**: 756–765.
433 Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Schteingart DE. Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biol Psychiatry* 1999; **46**: 1595–1602.
434 Kates WR, Abrams MT, Kaufmann WE, Breiter SN, Reiss AL. Reliability and validity of MRI measurement of the amygdala and hippocampus in children with fragile X syndrome. *Psychiatry Res* 1997; **75**: 31–48.
435 Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC *et al.* Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA* 2000; **284**: 1939–1947.
436 Vythilingam M, Anderson ER, Goddard A, Woods SW, Staib LH, Charney DS *et al.* Temporal lobe volume in panic disorder—a quantitative magnetic resonance imaging study. *Psychiatry Res* 2000; **99**: 75–82.
437 Uchida RR, Del-Ben CM, Santos AC, Araujo D, Crippa JA, Guimaraes FS *et al.* Decreased left temporal lobe volume of panic patients measured by magnetic resonance imaging. *Braz J Med Biol Res* 2003; **36**: 925–929.
438 Camicioli R, Moore MM, Kinney A, Corbridge E, Glassberg K, Kaye JA. Parkinson's disease is associated with hippocampal atrophy. *Mov Disord* 2003; **18**: 784–790.
439 Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP *et al.* Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1996; **53**: 607–616.
440 Laakso MP, Vaurio O, Koivisto E, Savolainen L, Eronen M, Aronen HJ *et al.* Psychopathy and the posterior hippocampus. *Behav Brain Res* 2001; **118**: 187–193.
441 Giordano GD, Renzetti P, Parodi RC, Foppiani L, Zandrino F, Giordano G *et al.* Volume measurement with magnetic resonance imaging of hippocampus-amygdala formation in patients with anorexia nervosa. *J Endocrinol Invest* 2001; **24**: 510–514.
442 Nakano T, Wenner M, Inagaki M, Kugaya A, Akechi T, Matsuoka Y *et al.* Relationship between distressing cancer-related recollections and hippocampal volume in cancer survivors. *Am J Psychiatry* 2002; **159**: 2087–2093.
443 Merke DP, Fields JD, Keil MF, Vaituzis AC, Chrousos GP, Giedd JN. Children with classic congenital adrenal hyperplasia have decreased amygdala volume: potential prenatal and postnatal hormonal effects. *J Clin Endocrinol Metab* 2003; **88**: 1760–1765.
444 Archibald SL, Fennema-Notestine C, Gamst A, Riley EP, Mattson SN, Jernigan TL. Brain dysmorphology in individuals with severe prenatal alcohol exposure. *Dev Med Child Neurol* 2001; **43**: 148–154.
445 Rosas HD, Koroshetz WJ, Chen YI, Skeuse C, Vangel M, Cudkowicz ME *et al.* Evidence for more widespread cerebral pathology in early HD: An MRI-based morphometric analysis. *Neurology* 2003; **60**: 1615–1620.
446 Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, Corfield DR. Changes in brain morphology associated with obstructive sleep apnea. *Sleep Med* 2003; **4**: 451–454.
447 Geuze E, Vermetten E, Bremner JD. MR-based *in vivo* hippocampal volumetrics: 1. Review of methodologies currently employed. *Mol Psychiatry* 2004, submitted.